Managed Care Dossier
For Presentation to:

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Executive Summary

Asthma is a common chronic condition in this country. Based on the 2006 U.S. National Health Interview Survey (NHIS) there were 16.1 million adults with asthma (approximately 7.3% of the U.S. adult population) and 6.8 million children with asthma (approximately 9.4% of the U.S. pediatric population).[Pleis and Bloom, NHIS 2006] In the same report, it was noted that lifetime prevalence of asthma was estimated to be 34.1 million Americans, with the highest prevalence rates in children 5-17 years of age.[ALA 2007]

In 2007, it is estimated that the total direct and indirect costs for asthma amounted to $19.7 billion: direct and indirect medical expenditures accounted for $14.7 billion and $5.0 billion, respectively. The single largest expenditure ($6.2 billion) is for prescription drugs, followed by hospitalizations ($4.7 billion).[ALA 2007]

Uncontrolled asthma interferes with daily activities, including attending school, going to work, and lost productivity. In 2003, among those who reported at least one asthma attack in the previous year, children 5-17 years of age missed 12.8 million school days due to asthma, and adults 18 years of age and over who were currently employed missed 10.1 million work days due to asthma.[ALA 2007] It should be noted that the figure for adults does not include days of work missed due to caring for an asthmatic child.

There are a number of pharmacologic treatment options available for asthma. While most of these medications have been useful in the management of asthma, there continues to be unmet needs, especially for those who experience side effects, cannot tolerate medications, or are poorly controlled by existing medications.

The introduction and adoption of inhaled corticosteroids (ICS) for the management of asthma has had a profound impact on the disease as measured by acute exacerbations resulting in emergency room (ER) visits and hospitalizations. In addition, the introduction of ICSs has had an impact on the need for short acting beta agonists (SABA) and exacerbations. Even with these medications, there continue to be unmet needs in the treatment of asthma.

ALVESCO® (ciclesonide) Inhalation Aerosol is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and adolescent patients 12 years of age and older. ALVESCO is a prodrug. Following administration, the parent compound is enzymatically hydrolyzed to an active metabolite (desisobutyryl-ciclesonide) by esterases located in the bronchial tissue. ALVESCO contains an HFA propellant and is formulated as a solution, delivering an 80 or 160 mcg dose of ciclesonide per inhalation.

The efficacy and safety of ALVESCO has been well studied worldwide (see Section 2.0, Supporting Clinical and Economic Information). Six clinical trials evaluating efficacy were performed with ALVESCO that were the basis of the product's U.S. FDA approval. In the twice-daily trials, approximately 800 patients (12 years of age and older) with asthma of varying severity received the approved doses. Additional safety evaluations have also demonstrated the long-term safety and efficacy, the minimal effects on hypothalamic-pituitary-adrenal (HPA) axis function, and the ophthalmologic safety of

ALVESCO. The efficacy and safety results of clinical trials evaluating ALVESCO Inhalation Aerosol are more fully described in Section 2.2 of this document.

ALVESCO is available in two strengths (80 mcg and 160 mcg) and the recommended dosing frequency allows for twice-daily administration of one or two inhalations, according to individual patient requirements. ALVESCO is supplied as an HFA metered-dose inhaler and contains a dose-indicator.

ALVESCO has been approved in over 40 countries and is commercially available in at least 30 with more launches expected in 2008. The product is marketed by Nycomed outside of the U.S. Sepracor Inc.'s rights to market and distribute ALVESCO Inhalation Aerosol are in the U.S. only.[Sepracor Press Release]

Product Information

1.1 Product Description

Generic and Brand Name; Therapeutic Class

The drug component of ALVESCO 80 mcg Inhalation Aerosol, and ALVESCO 160 mcg Inhalation Aerosol is ciclesonide, a non-halogenated glucocorticoid used as an inhaled corticosteroid (ICS) for asthma. Ciclesonide is a white to yellow-white powder. It is soluble in dehydrated alcohol, acetone, dichloromethane, and chloroform.[PI]

Dosage Forms, Strengths, Package Sizes, NDC Codes, and Prices

ALVESCO Inhalation Aerosol is a pressurized, metered-dose aerosol unit fitted with a dose indicator. ALVESCO is intended for oral inhalation only. Each unit contains a solution of ciclesonide in propellant HFA-134a (1,1,1,2 tetrafluoroethane) and ethanol. ALVESCO 80 mcg delivers 100 mcg from the valve and 80 mcg of ciclesonide from the actuator. ALVESCO 160 mcg delivers 200 mcg from the valve and 160 mcg of ciclesonide from the actuator. Both products deliver 50 microliters (59.3 milligrams) of solution as a fine particle mist from the valve with each actuation. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between the actuation of the device and inspiration through the delivery system. ALVESCO should be "primed" by actuating 3 times prior to using the first dose from a new canister or when the inhaler has not been used for more than 10 days. Shaking prior to use is not required. Avoid spraying in the eyes or face while priming ALVESCO.[PI]

This product does not contain chlorofluorocarbons (CFCs).

ALVESCO is available in the following strengths and canister sizes.

Table 1.1.1: ALVESCO Availability and Prices

Micrograms per Inhalation	Number of Inhalations per Canister	Canister Weight	NDC Number	WAC*
ALVESCO 80 mcg	60	6.1g	63402-711-01	$130.00
ALVESCO 160 mcg	60	6.1g	63402-712-01	$130.00

*Wholesaler acquisition cost.

ALVESCO 80 mcg Inhalation Aerosol is supplied with a brown plastic actuator with a red dust cap and patient instructions. Each actuation of the inhaler delivers 80 mcg of ciclesonide from the actuator.

ALVESCO 160 mcg Inhalation Aerosol is supplied with a red plastic actuator with a red dust cap and patient instructions. Each actuation of the inhaler delivers 160 mcg of ciclesonide from the actuator.

ALVESCO canisters are for use with ALVESCO Inhalation Aerosol actuators only. The actuators are fitted with a dose indicator and should not be used with other inhalation aerosol medications. The correct amount of medication in each inhalation cannot be assured after 60 inhalations from the canister when the dose indicator display window shows zero, even though the canister is not completely empty. The canister should be discarded when the dose indicator display window shows zero. Shaking prior to use is not required. **Store at 25°C (77°F).**

Excursions between 15° and 30°C (59° and 86°F) are permitted (see USP). For optimal results, the canister should be at room temperature when used. Keep out of reach of children.

AHFS Drug Classification

68:04 Adrenals

FDA Approved Indications; Approval Date

ALVESCO is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and adolescents patients 12 years of age and older.

ALVESCO is NOT indicated for the relief of acute bronchospasm.

ALVESCO is NOT indicated for children under 12 years of age.

ALVESCO was approved by the U.S. FDA on January 10, 2008.

Other Studied Indications, Including Pending Indications, and Other Non-labeled Uses

There are no studies underway with ALVESCO Inhalation Aerosol for other disease indications.

Pharmacology

Mechanism of Action

Ciclesonide, is a prodrug, that is enzymatically hydrolyzed to a pharmacologically active metabolite, C21-desisobutyryl-ciclesonide (des-ciclesonide or RM1) following oral inhalation. Des-ciclesonide has anti-inflammatory activity with affinity for glucocorticoid receptors that is 120 times greater than the parent compound and 12 times greater than dexamethasone. The clinical significance of these findings is unknown.

The precise mechanisms of corticosteroid action in asthma are unknown. Inflammation is recognized as an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma. Though effective for the treatment of asthma, corticosteroids do not affect asthma symptoms immediately. Individual patients will experience a variable time to onset and degree of symptom relief. Maximum benefit may not be achieved for four weeks or longer after starting treatment. When corticosteroids are discontinued, asthma stability may persist for several days or longer.[PI]

Pharmacodynamics

The effect of ciclesonide by oral inhalation on the HPA axis was assessed in adults with mild asthma in a 29-day placebo controlled study. Twenty-four-hour urinary free cortisol was assessed in a total of 59 adults who were randomized to 320 mcg or 640 mcg ALVESCO, a comparator corticosteroid, or placebo twice daily. At the end of 29 days of treatment, the mean (SE) change from baseline in 24 hr urinary free cortisol was –8.69 (5.6) mcg/day, -4.01 (5.03) mcg/day, and –8.84 (5.02) mcg/day for the placebo, ALVESCO 640 mcg/day, and ALVESCO 1280 mcg/day, respectively. The difference from placebo for the change from baseline in 24 hr urinary cortisol was +4.7 mcg/day [95% CI: -10.58; 19.93] and –0.16 mcg/day [95% CI: -15.20; 14.89] for the 640 mcg/day or 1280 mcg/day treatments, respectively. The effects observed with the comparator corticosteroid validate the sensitivity of the study to assess the effect of ciclesonide on the HPA axis.[PI] For a more complete description of this trial, refer to the summary of Szefler, et al. in the Clinical and Economic Evaluations section of this dossier.

Additionally, the potential systemic effect of ALVESCO on the HPA axis was assessed in 164 adults with mild to moderate persistent asthma in a 12-week study with oral inhalation of ALVESCO (doses of 320 mcg once daily in the evening or 320 mcg twice daily) compared with placebo or active control (fluticasone propionate 440 mcg twice daily). No statistically significant differences were observed between ALVESCO, comparator, and placebo groups in baseline urinary free cortisol. After 12-week treatment, the percent mean reduction in 24-hour urinary free cortisol from baseline to Week 12 was not statistically significant in the ALVESCO groups compared to placebo. However, there was a mean decrease of 60.8% from baseline to Week 12 in the comparator group compared to 19.8% mean decrease in the placebo group (p=0.01).[Lipworth, p.469]

Pharmacokinetics

Absorption

Ciclesonide and des-ciclesonide have negligible oral bioavailability (both are less than 1%) due to low gastrointestinal absorption and high first-pass metabolism. Serum concentrations of ciclesonide and des-ciclesonide were measured and compared following oral inhalation of 1280 mcg ALVESCO and intravenous administration of 800 mcg ciclesonide. The absolute bioavailability of ciclesonide was 22% and the relative

systemic exposure of des-ciclesonide was 63%. The mean Cmax for des-ciclesonide was 1.02 ng/mL (range 0.6-1.5 ng/mL) in asthmatic patients following a single dose of 1280 mcg by oral inhalation. The mean Cmax (0.369 ng/mL) and AUC0-∞ (2.18 ng*hr/mL) of des-ciclesonide following multiple dose administration of ciclesonide 320 mcg once daily increased up to 26% compared to single dose administration.[PI]

Distribution

Following intravenous administration of 800 mcg of ciclesonide, the volumes of distribution of ciclesonide and des-ciclesonide were approximately 2.9 L/kg and 12.1 L/kg, respectively. The percentage of ciclesonide and des-ciclesonide bound to human plasma proteins averaged ≥ 99% each, with ≤ 1% of unbound drug detected in the systemic circulation. Des-ciclesonide is not significantly bound to human transcortin.[PI]

Metabolism

Ciclesonide is hydrolyzed to a biologically active metabolite, des-ciclesonide, by esterases. Des-ciclesonide undergoes further metabolism in the liver to additional metabolites mainly by the cytochrome P450 (CYP) 3A4 isozyme and to a lesser extent by CYP2D6. The full range of potentially active metabolites of ciclesonide has not been characterized. After intravenous administration of ^{14}C-ciclesonide, 19.3% of the resulting radioactivity in the plasma is accounted for by ciclesonide or des-ciclesonide; the remainder may be a result of other, as yet, unidentified multiple metabolites.[PI]

Elimination

Following intravenous administration of 800 mcg of ciclesonide, the clearances of ciclesonide and des-ciclesonide were high (approximately 152 L/hr and 228 L/hr, respectively). ^{14}C-labeled ciclesonide was predominantly excreted via the feces after intravenous administration (66%) indicating that excretion through bile is the major route of elimination. Approximately 20% or less of des-ciclesonide was excreted in the urine. The mean half life of ciclesonide and des-ciclesonide was 0.71 hours and 6 to 7 hours respectively. T_{max} of desciclesonide occurs at 1.04 hours following inhalation of ciclesonide.[PI]

Special Populations:

Population pharmacokinetic analysis showed that characteristics of des-ciclesonide after oral inhalation of ciclesonide were not appreciably influenced by a variety of subject characteristics such as body weight, age, race, and gender. [PI]

Renal Insufficiency:

Studies in renally-impaired patients were not conducted since renal excretion of des-ciclesonide is a minor route of elimination (≤ 20%).[PI]

Hepatic Insufficiency:

Compared to healthy subjects, the systemic exposure of des-ciclesonide (C_{max} and AUC) in patients with moderate to severe liver impairment increased in the range of 1.4 to 2.7 fold after 1280 mcg ex-actuator ciclesonide by oral inhalation. Dose adjustment in patients with liver impairment is not necessary.[PI]

Pediatric:
In 2 clinical safety and efficacy studies conducted in patients 4 to 11 years of age with asthma, population pharmacokinetic samples were obtained in 53 patients for pharmacokinetic analysis. In these pediatric patients, treated with daily doses of 40, 80 or 160 mcg of ALVESCO, the median (min, max) C_{max} values of des-ciclesonide were 41 pg/mL (not detectable, 146 pg/mL) (n=11), 113 pg/mL (35, 237 pg/mL) (n=13) and 128 pg/mL (12, 357 pg/mL) (n=14), respectively.[PI]

Contraindications

ALVESCO is contraindicated in:
Status Asthmaticus
ALVESCO is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity
ALVESCO is contraindicated in patients with known hypersensitivity to ciclesonide or any of the ingredients. Rare cases of hypersensitivity reactions with manifestations such as angioedema, with swelling of the lips, tongue and pharynx, have been reported.[PI]

Warnings and Precautions

Local Effects
In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* occurred in 32 of 3038 patients treated with ALVESCO. Of the 32 reported cases, 20 occurred in 1394 patients treated with a total daily dose of 320 mcg of ALVESCO or higher. Most cases of candida infection were mild to moderate. When such an infection develops, it should be treated with appropriate local or systemic (i.e. oral antifungal) therapy while remaining on treatment with ALVESCO, but at times therapy with ALVESCO may need to be interrupted. Patients should rinse the mouth after inhalation of ALVESCO.[PI]

Acute Asthma Episodes
ALVESCO is not a bronchodilator and is not indicated for rapid relief of bronchospasm or other acute episodes of asthma. Patients should be instructed to contact their physician immediately if episodes of asthma not responsive to their usual doses of bronchodilators occur during the course of treatment with ALVESCO. During such episodes, patients may require therapy with oral corticosteroids.[PI]

Immunosuppression
Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster

immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered. Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.[PI]

Transferring Patients from Systemic Corticosteroid Therapy

Particular care is needed for patients who are transferred from systemically active corticosteroids to ALVESCO because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although ALVESCO may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of corticosteroid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a medical identification card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to ALVESCO. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during ALVESCO. Lung function (FEV_1 or AM PEFR), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic steroid therapy to ALVESCO may unmask allergic conditions previously suppressed by the systemic steroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and eosinophilic conditions.

During withdrawal from oral steroids, some patients may experience symptoms of systemically active steroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.[PI]

Hypercorticism and Adrenal Suppression
ALVESCO will often help control asthma symptoms with less suppression of HPA function than therapeutically similar oral doses of prednisone. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing ALVESCO. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response. It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear in a small number of patients particularly when ALVESCO is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of ALVESCO should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma.[PI]

Reduction in Bone Mineral Density
Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term outcomes is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, or chronic use of drugs that can reduce bone mass (e.g. anticonvulsants and oral corticosteroids) should be monitored and treated with established standards of care.[PI]

Effect on Growth
Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving ALVESCO routinely (e.g. via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including ALVESCO titrate each patients' dose to the lowest dosage that effectively controls his/her symptoms.[PI]

Glaucoma and Cataracts
Glaucoma, increased intraocular pressure, and cataracts have been reported following the administration of inhaled corticosteroids including ALVESCO. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

In a comparator control study of one year treatment duration, 743 patients 18 years of age and older (mean age 43.1 years) with moderate persistent asthma were treated with ALVESCO 320 mcg twice daily and 742 were treated with a labeled dose of a comparator inhaled corticosteroid appropriate for the patient population. Patients had an ophthalmology examination that included visual acuity, intraocular pressure measurement, and a slit lamp examination at baseline, 4, 8 and 12 months. Lens opacities were graded using the Lens Opacification System III. After 52 weeks, CLASS I effects (minimally detected changes) were recorded in 36.1% of the ALVESCO-treated patients and in 38.4% of patients treated with the comparator inhaled corticosteroid. The more

severe CLASS III effects were recorded in 8.1% of the ALVESCO treated patients and 9.2% of patients treated with the comparator inhaled corticosteroid. Of those patients having a CLASS III effect, the incidence of posterior sub-capsular opacities was 0.9% and 0.5% in the ALVESCO- and comparator-treated patients respectively.[PI]

Bronchospasm
As with other inhaled asthma medications, bronchospasm, with an immediate increase in wheezing, may occur after dosing. If bronchospasm occurs following dosing with ALVESCO, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with ALVESCO should be discontinued and alternative treatment should be instituted.[PI]

Use in Specific Populations
Pregnancy
Teratogenic Effects: Pregnancy Category C

Oral administration of ciclesonide in rats up to 900 mcg/kg/day (approximately 10 times the maximum human daily inhalation dose based on mcg/m^2/day) produced no teratogenicity or other fetal effects. However, subcutaneous administration of ciclesonide in rabbits at 5 mcg/kg/day (less than the maximum human daily inhalation dose based on mcg/m^2/day) or greater produced fetal toxicity. This included fetal loss, reduced fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications, and skin effects. No toxicity was observed at 1 mcg/kg (less than the maximum human daily inhalation dose based on mcg/m^2).

There are no adequate and well-controlled studies in pregnant women. ALVESCO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Non-teratogenic Effects
Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.[PI]

Nursing Mothers
It is not known if ciclesonide is secreted in human milk. However, other corticosteroids are excreted in human milk. In a study with lactating rats, minimal, but detectable levels of ciclesonide were recovered in milk. Caution should be used when ALVESCO is administered to nursing women.[PI]

Pediatric Use
The safety and effectiveness of ALVESCO in children under 12 years of age have not been established.

Two randomized double-blind placebo-controlled studies were conducted to evaluate the efficacy of ALVESCO 40, 80, or 160 mcg administered once daily for 12 weeks in patients 4 to 11 years of age with asthma. These studies included 1018 patients previously using either controller therapy (predominately inhaled corticosteroids) or reliever therapy (bronchodilator therapy alone). The patients had a mean baseline percent predicated FEV_1 of 68%. The primary efficacy endpoint was morning pre-dose FEV_1. Other measures of efficacy included AM PEF, asthma symptoms, and rescue albuterol use. The studies showed inconsistent results and do not establish the efficacy of ALVESCO in patients 4 to 11 years of age.[PI]

The safety of ALVESCO was evaluated in 957 children between the ages of 4 and 11 who were treated with ALVESCO in the two controlled clinical studies, 2 open label one-year safety extensions of the controlled clinical studies, and one open label safety study. In the controlled studies, the distribution of adverse events in the ALVESCO and placebo groups was similar. The type of adverse events reported were similar to events reported in this patient population with other inhaled corticosteroids. The open label safety studies compared the safety of ALVESCO in doses up to 160 mcg once daily with an orally inhaled corticosteroid comparator. The types of adverse events seen were similar to those seen in the 12-week controlled studies.[PI]

Controlled clinical studies have shown that orally inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately one centimeter per year (range 0.3 to 1.8 cm per year) and appears to be related to dose and duration of exposure. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height are unknown. The potential for "catch up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied. The growth of pediatric patients receiving orally inhaled corticosteroids including ALVESCO should be monitored routinely (e.g., via stadiometry).[PI]

A 52-week, multi-center, double-blind, randomized, placebo-controlled parallel-group study was conducted to assess the effect of orally inhaled ciclesonide on growth rate in 609 pediatric patients with mild persistent asthma, aged 5 to 8.5 years. Treatment groups included orally inhaled ciclesonide 40 mcg or 160 mcg or placebo given once daily. Growth was measured by stadiometer height during the baseline, treatment and follow-up periods. The primary comparison was the difference in growth rates between ciclesonide 40 and 160 mcg and placebo groups. Conclusions cannot be drawn from this study because compliance could not be assured. There was no difference in efficacy measures between the placebo and the ALVESCO groups. Ciclesonide blood levels were also not measured during the one-year treatment period. The potential growth effects of prolonged treatment with orally inhaled corticosteroids should be weighed against clinical benefits obtained and the availability of safe and effective noncorticosteroid treatment alternatives. To minimize the systemic effects of orally inhaled corticosteroids,

including ALVESCO, each patient should be titrated to his/her lowest effective dose.[PI] For a more detailed description of this trial, refer to the trial summary for Skoner et al. (Study Report 343) in the Clinical and Economic Evaluations section.

Geriatric Use
Clinical studies of ALVESCO did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.[PI]

Adverse Reactions

Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult and Adolescent Patients
Four trials included a total of 624 patients ages 12 years and older (359 females and 265 males) with asthma of varying severity who were treated with ALVESCO 80 mcg, 160 mcg, or 320 mcg twice daily for 12 to 16 weeks. These studies included patients previously using either controller therapy (predominantly inhaled corticosteroids) or reliever therapy (bronchodilator therapy alone). In these trials, the mean age was 39.1 years, and the majority of the patients (79.0%) were Caucasian. In these trials, 52.3%, 59.8% and 54.1% of the patients in the ALVESCO 80 mcg, 160 mcg, and 320 mcg treatment groups, respectively, had at least one adverse event compared to 58.0% in the placebo group. **Table 1.1.2** includes adverse reactions for the recommended doses of ALVESCO that occurred at an incidence of ≥ 3% in any of the ALVESCO groups and which were more frequent with ALVESCO compared to placebo.[PI]

Table 1.1.2: Adverse Reactions with ≥3% Incidence Reported in Patients ≥ 12 Years of Age with ALVESCO in US Placebo-Controlled Clinical Trials in Patients Previously on Bronchodilators and/or Inhaled Corticosteroids [PI]

Adverse Reaction	Placebo (N=507) %	ALVESCO 80 mcg BID (N=325) %	ALVESCO 160 mcg BID (N=127) %	ALVESCO 320 mcg BID (N=172) %
Headache	7.3	4.9	11.0	8.7
Nasopharyngitis	7.5	10.5	8.7	7.0
Sinusitis	3.0	3.1	5.5	5.2
Pharyngolaryngeal pain	4.3	4.3	2.4	4.7
Upper respiratory Inf.	6.5	7.1	8.7	4.1
Arthralgia	1.0	0.9	2.4	3.5
Nasal congestion	1.6	1.8	5.5	2.9
Pain in extremity	1.0	0.3	3.1	2.3
Back pain	2.0	0.6	3.1	1.2

The following adverse reactions occurred in these clinical trials using ALVESCO with an incidence of less than 1% and occurred at a greater incidence with ALVESCO than with placebo.

Infections and Infestations: Oral candidiasis
Respiratory Disorders: Cough
Gastrointestinal Disorders: Dry mouth, nausea.
General disorders and administrative site conditions: Chest discomfort
Respiratory, Thoracic, and Mediastinal Disorders: Dysphonia, dry throat [PI]

A fifth study was a 12-week clinical trial in asthma patients 12 years of age and older who previously required oral corticosteroids (average daily dose of oral prednisone of 12 mg/day), in which the effects of ALVESCO 320 mcg twice daily (n = 47) and 640 mcg twice daily (n = 49) were compared with placebo (n = 45) for the frequency of reported adverse reactions. The following adverse reactions occurred at an incidence of ≥ 3% in the ALVESCO-treated patients and were more frequent compared to placebo: sinusitis, hoarseness, oral candidiasis, influenza, pneumonia, nasopharyngitis, arthralgia, back pain, musculoskeletal chest pain, headache, urticaria, dizziness, gastroenteritis, face edema, fatigue, and conjunctivitis.[PI]

Long-Term Clinical Trials Experience
A total of 197 patients 12 years of age and older (82 males and 115 females) from one of the 12-week treatment placebo-controlled studies were re-randomized to ciclesonide 320 mcg twice daily and followed for one year. The safety profile from the one-year follow up was similar to that seen in the 12- and 16-week treatment studies.[PI] For more detail on this long-term trial, refer to the summary for Study Report 323/324 LT trial in the Clinical and Economic Evaluations section.

Pediatric Patients

Pediatric Patients 4 To 11 Years of Age

The safety of ALVESCO in pediatric patients 4 to 11 years of age was evaluated in two studies in which ALVESCO 40 mcg, 80 mcg, and 160 mcg was administered once daily for 12 weeks.[PI] For more detail on these trials, refer to the summary for Gelfand et al. (Study Reports 341 and 342) in the Clinical and Economic Evaluations section.

Long-Term Clinical Trials Experience

Long term safety information for pediatric patients 4 to 11 years of age was obtained from three open-label one year safety studies.[PI] For more information on two of these trials, the safety extensions of the pivotal trials submitted for the pediatric approval of ALVESCO Inhalation Aerosol, refer to the summaries for 341 LT and 342 LT in the Clinical and Economic Evaluations section.

Please note that ALVESCO Inhalation Aerosol is NOT indicated in children under the age of 12 years.

Pediatric Patients under 4 Years of Age

Studies have not been conducted in patients under 4 years of age.[PI]

Post-marketing Experience

In addition to adverse reactions identified from clinical trials, the following adverse reactions have been identified during worldwide post-marketing use of ALVESCO:

Immune System Disorders: Immediate or delayed hypersensitivity reactions such as angioedema with swelling of the lips, tongue and pharynx.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.[PI]

Overdosage

Chronic overdosage may result in signs/symptoms of hypercorticism. ALVESCO was well tolerated following inhalation by healthy subjects of single doses of 2880 mcg. A single oral dose of up to 10 mg of ciclesonide in healthy subjects was well tolerated and serum cortisol levels were virtually unchanged in comparison with placebo treatment. Adverse reactions were of mild or moderate severity.

The median lethal doses in mice and rats after single oral and intraperitoneal administration were >2000 mg/kg and >200 mg/kg, respectively. These doses are >12000 and >2500 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis.[PI]

Interactions

In a drug interaction study, co-administration of orally inhaled ciclesonide and oral ketoconazole, a potent inhibitor of cytochrome P450 3A4, increased the exposure (AUC) of the ciclesonide active metabolite, des-ciclesonide, by approximately 3.6-fold at steady state, while levels of ciclesonide remained unchanged.

In another single-dose drug interaction study, co-administration of orally inhaled ciclesonide and oral erythromycin, an inhibitor of cytochrome P450 3A4, had no effect on the pharmacokinetics of either ciclesonide and its active metabolite, des-ciclesonide, or erythromycin.

Based on *in vitro* studies in human liver microsomes, des-ciclesonide had no significant potential to inhibit or induce the metabolism of other drugs. Based on *in vitro* human hepatocyte studies, ciclesonide and des-ciclesonide had no potential to induce major CYP450 isozymes.

In vitro studies demonstrated that the plasma protein binding of des-ciclesonide was not affected by warfarin or salicylic acid, indicating no potential for protein binding-based drug interactions.

In a population pharmacokinetic analysis including 98 subjects, co-administration of ALVESCO and albuterol had no effect on the pharmacokinetics of des-ciclesonide.

Concomitant administration of ALVESCO (640 mcg) and formoterol (24 mcg) did not change the pharmacokinetics of either des-ciclesonide or formoterol.[PI]

Dosing and Administration

ALVESCO should be administered by the orally inhaled route. Prime ALVESCO Inhalation Aerosol before using for the first time by actuating 3 times prior to using the first dose from a new canister or when the inhaler has not been used for more than 10 days. Individual patients will experience a variable time to onset and degree of symptom relief. Maximum benefit may not be achieved for four weeks or longer after initiation. After asthma stability has been achieved, it is desirable to titrate to the lowest effective dosage to reduce the possibility of side effects. For patients who do not respond adequately to the starting dose after 4 weeks of therapy, higher doses may provide additional asthma control. The safety and efficacy of ALVESCO when administered in excess of the highest recommended doses has not been established.[PI]

Recommended Dosages
The recommended starting dose and the highest recommended dose of ALVESCO Inhalation Aerosol are listed in the following table.

Table 1.1.3: ALVESCO Dosing Regimens [PI]

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Patients ≥ 12 years who received bronchodilators alone	80 mcg twice daily	160 mcg twice daily
Patients ≥ 12 years who received inhaled corticosteroids	80 mcg twice daily	320 mcg twice daily
Patients ≥ 12 years who received oral corticosteroids[1]	320 mcg twice daily	320 mcg twice daily

[1]Prednisone should be reduced gradually, no faster than 2.5 mg/day on a weekly basis, beginning after at least 1 week of therapy with ALVESCO. Patients should be carefully monitored for signs of asthma instability, including monitoring of serial objective measures of airflow, and for signs of adrenal insufficiency during steroid taper and following discontinuation of oral corticosteroid therapy.

Access Issues

There are no anticipated supply or other access problems.

Current/Anticipated Market Share Information

There were approximately 11 million prescriptions for inhaled corticosteroids written in the United States in 2007.[IMS Health NPA2007] ALVESCO will be available to primary care physicians, pulmonologists, allergists, and pediatricians beginning in late 2008.

Co-prescribed/Concomitant Therapies

Inhaled corticosteroids, including ALVESCO, may be used concomitantly with a number of other agents as described later in the **Relevant Treatment Guidelines** section of this section.

Comparison with Related Agents

There are a number of related inhaled corticosteroids that can be compared to ALVESCO. The following table summarizes a variety of parameters for the most frequently prescribed medications for asthma therapy, based primarily on information from these products' respective Prescribing Information. The information included is not meant to imply similar efficacy and/or safety among agents.

Table 1.1.4: Comparison of Most Frequently Prescribed Agents for Asthma Therapy

Drug	Formulations	Dose/Actuations	Weight and Actuations per Container	Cost (WAC)*	Indication(s)	Approved Dosing
ALVESCO® (ciclesonide) Inhalation Aerosol May 2008	Solution HFA MDI	80 mcg, 160 mcg	80 mcg (6.1 g)- 60 160 mcg (6.1 g)- 60	$130.00	Maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients **12 years of age and older**.	**Adults (12 and older):** *Bronchodilators alone*- start 80 mcg BID, highest 160 mcg BID *Inhaled corticosteroids*- start 80 mcg BID, highest 320 mcg BID *Oral corticosteroids*- start 320 mcg BID, highest 320 mcg BID
QVAR® (beclomethasone dipropionate HFA) Inhalation Aerosol Oct 2006	Solution HFA MDI	40 mcg, 80 mcg	7.3 g, 100 7.3 g, 100	$59.65, $75.17	In the maintenance treatment of asthma as prophylactic therapy in patients **5 years of age and older**. Also for asthma patients who require systemic corticosteroid administration, where adding QVAR may reduce or eliminate the need for the systemic corticosteroids.	**Adults (12 and older):** *Bronchodilators alone*- start 40-80 mcg BID, highest 320 mcg BID *Inhaled corticosteroids*- start 40-160 mcg BID, highest 320 mcg BID **Children (5-11):** *Bronchodilators alone*- start 40 mcg BID, highest 80 mcg BID *Inhaled corticosteroids*- start 40 mcg BID, highest 80 mcg BID

Drug	Formulations	Dose/Actuations	Weight and Actuations per Container	Cost (WAC)*	Indication(s)	Approved Dosing
Pulmicort Flexhaler™ (budesonide inhalation powder) Aug 2007	Suspension HFA MDI	90 mcg, 180 mcg	90 mcg- 60 180 mcg- 60	$85.25, $114.14	For the maintenance treatment of asthma as prophylactic therapy in adults and pediatric patients **6 years of age or older**. Also for patients requiring oral corticosteroid therapy for asthma. Many of those patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.	**Adults (18 and older):** Start 180-360 mcg BID, highest 720 mcg BID **Children (6-17):** Start 180-360 mcg BID, highest 360 mcg BID
Pulmicort Respules® (budesonide inhalation suspension) June 2007	Inhalation Suspension	0.25 mg/2 mL, 0.5 mg/2 mL, 1.0 mg/2 mL	30 respules/ carton	Per respule, month if QD, month if BID: 0.25 mg/ 2 mL: $5.05 $151.50 $303.00 0.5 mg/ 2 mL: $5.94 $178.20 $356.40 1.0 mg/ 2 mL: $11.88 $356.40 $712.80	For the maintenance treatment of asthma and as prophylactic therapy in **children 12 months to 8 years of age.**	**Children (12 months to 8 years):** *Bronchodilators alone*- 0.5 mg QD or BID in divided doses, highest daily 0.5 mg *Inhaled corticosteroids*- 0.5 mg QD or BID in divided doses, highest daily 1.0 mg *Oral corticosteroids*- 0.5 mg BID or 1.0 mg QD, highest daily 1.0 mg

Drug	Formulations	Dose/Actuations	Weight and Actuations per Container	Cost (WAC)*	Indication(s)	Approved Dosing
FLOVENT® HFA (fluticasone propionate) Inhalation Aerosol July 2008	Suspension HFA MDI	44 mcg, 110 mcg, 220 mcg	44 mcg (10.6 g)- 120 110 mcg (12 g)- 120 220 mcg (12 g)- 120	$86.06, $111.21, $172.73	For the maintenance treatment of asthma as prophylactic therapy in patients **4 years of age and older**. Also for patients requiring oral corticosteroid therapy for asthma. Many of these patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.	**Adults (12 and older):** *Bronchodilators alone*- start 88 mcg BID, highest 440 mcg BID *Inhaled corticosteroids*- start 88-220 mcg BID, highest 440 mcg BID *Oral corticosteroids*- start 440 mcg BID, highest 880 mcg BID **Children (4-11):** Start 88 mcg BID and highest 88 mcg BID
ASMANEX®, TWISTHALER® (mometasone furoate inhalation powder) Feb 2008	Dry-powder inhaler (DPI)	110 mcg, 220 mcg	110 mcg- 7 units 110mcg- 30 units 220 mcg- 14 units 220 mcg- 30 units 220 mcg- 60 units 220 mcg- 120 units	N/A, $92.05, $73.96, $97.19, $105.35, $150.98	For the maintenance treatment of asthma as prophylactic therapy in patients **4 years of age and older**.	**Adults (12 and older):** *Bronchodilators alone*- start 220 mcg QD_{PM}, highest 440 mcg *Inhaled corticosteroids*- start 220 mcg QD_{PM}, highest 440 mcg *Oral corticosteroids*- start 440 mcg BID, highest 880 mcg **Children (4-11):** Start 110 mcg QD_{PM}, highest 110 mcg

Drug	Formulations	Dose/Actuations	Weight and Actuations per Container	Cost (WAC)*	Indication(s)	Approved Dosing
SYMBICORT® (budesonide and formoterol fumarate dehydrate) Inhalation Aerosol May 2007	HFA MDI	80 mcg/4.5 mcg, 160 mcg/4.5 mcg	80 mcg/ 4.5 mcg (6.9 g)- 60 80 mcg/ 4.5 mcg (10.2 g)- 120 160 mcg/ 4.5 mcg (6.0 g)- 60 160 mcg/ 4.5 mcg (10.2 g)- 120	$139.81, $159.80	For the long-term maintenance treatment of asthma in patients **12 years of age and older**.	**Adults (12 and older):** *Bronchodilators alone-* start 2 inhalations of 80/4.5 or 160/4.5 BID *Inhaled corticosteroids low-mod dose-* start 2 inhalations of 80/4.5 BID *Inhaled corticosteroids mod-high-* start 2 inhalations of 160/4.5 BID *Max dose-* 640/18 mcg per day
ADVAIR DISKUS® (fluticasone propionate and salmeterol inhalation powder) April 2008	Dry-powder inhaler (DPI)	100 mcg/50 mcg, 250 mcg/50 mcg, 500 mcg/50 mcg	100 mcg/ 50 mcg- (60 blisters) 250 mcg/ 50 mcg- (60 blisters) 500 mcg/ 50 mcg- (60 blisters)	$139.73 $173.60 $273.49	For the long-term, twice-daily, maintenance treatment of asthma in patients **4 years of age and older**.	**Adults (12 and older):** 1 inhalation of 100/50, 250/50, or 500/50 BID **Children (4-11):** 1 inhalation of 100/50 BID

Drug	Formulations	Dose/Actuations	Weight and Actuations per Container	Cost (WAC)*	Indication(s)	Approved Dosing
SINGULAIR® (montelukast sodium) July 2008	Tablets, chewable tablets, oral granules	10 mg tablet, 4 mg and 5 mg chewable tablet, packet of 4 mg granules	10 mg tablet- (30, 90, blister pack of 100, bulk 8000) 5 mg tablet- (30, 90, blister pack of 100, bulk 1000) 4 mg tablet- (30, 90, blister pack of 100) 4 mg granule packets- (30)	For 30 day supply- $97.24 for all strengths	For the prophylactic and chronic treatment of asthma in adults and pediatric patients **12 months of age and older**. For prevention of exercise-induced bronchoconstriction in patients **15 years of age and older**.	**Adults (15 and older):** One 10 mg tablet QD **Children (6-14):** One 5 mg tablet QD **Children (2-5):** One 4 mg tablet or 4 mg granule packet QD **Children (6-23 months):** One 4 mg granule packet QD

*WAC = Wholesale Acquisition Cost

1.2 Place of ALVESCO in Therapy

Epidemiology and Relevant Risk Factors

Asthma is a common chronic condition in the United States, and its incidence, prevalence and severity are increasing. The U.S. National Health Interview Survey (NHIS) reported that in 2006, 22.9 million people or approximately 7.8% of the U.S. population currently had asthma. In 2006, 12.4 million persons or 4.2% of people had at least one asthma attack in the previous year. In 2006, an estimated 11.6% of persons or 34.1 million people had ever been diagnosed with asthma during their lifetime.[ALA 2007]

According to the NHIS survey, children had a higher prevalence of asthma than did adults; 9.4% of children (6.8 million) had asthma in 2006 compared to 7.3% of adults (16.1 million).[Pleis, Bloom NHIS 2006] In terms of gender, females had a 23% higher prevalence rate than males although this pattern was reversed among children aged 0-17 years. The asthma prevalence for boys (10.9%) was 46% higher than for girls (7.5).[ALA 2007]

Asthma disproportionately affects ethnic minorities. In 2006, the current prevalence rate was 23.8% higher in blacks than in whites (9.4% and 7.6%, respectively). There are numerical differences in prevalence between races. In 2006, 2.8 million Hispanic Americans reported current prevalence of asthma. The prevalence rates in Hispanics were lower than Non-Hispanic blacks and somewhat lower than Non-Hispanic whites in 2006. There is evidence that Puerto Ricans may have higher rates of asthma than other Hispanic subgroups and non-Hispanic whites.[ALA 2007] These trends may be due to disparities in socioeconomic status. Socioeconomic factors, such as living in an inner city and low socioeconomic status increases the risk for asthma-related death.[NHLBI EPR-3]

In 2004, 3,816 people died from asthma with more casualties occurring in females. In 2004, 141 children 14 years of age or younger died from asthma. Of the deaths in asthma patients, 2,658 were in whites and 1,158 were in other races (1,008 of those deaths in other races were in blacks).[ALA 2007]

The two major environmental risk factors for the development, persistence, and possibly the severity of asthma include airborne allergens and viral respiratory infections. Additional environmental factors currently being studied that may affect asthma include exposure to second-hand tobacco smoke in infancy and in-utero, air pollution, and diet.[NHLBI EPR-3]

Pathophysiology

Asthma is a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation. The National Asthma Education and Prevention Program (NAEPP) uses the following working definition of asthma as a guide to describing asthma and identifying treatment directions:

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, neutrophils (especially in sudden onset, fatal exacerbations, occupational asthma, and patients who smoke), T lymphocytes, macrophages, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of coughing (particularly at night or early in the morning), wheezing, breathlessness, and chest tightness. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. Socioeconomic factors, such as living in an inner city and low socioeconomic status increases the risk for asthma-related death.[NHLBI EPR-3]

Airflow limitation is caused by a variety of changes in the airway, all influenced by airway inflammation: [NHLBI EPR-3]

- Bronchoconstriction- bronchial smooth muscle contraction that quickly narrows the airways in response to exposure to a variety of stimuli, including allergens or irritants
- Airway hyperresponsiveness- an exaggerated bronchoconstrictor response to stimuli
- Airway edema- as the disease becomes more persistent and inflammation becomes more progressive, edema, mucus hypersecretion, and formation of inspissated mucus plugs further limit airflow

Table 1.2.1: Asthma Triggers[Kelly]

Category	**Examples of Specific Triggers**
Allergens	Animal dander, house dust mites, fungal spores, airborne pollens
Environmental Issues	Cool dry air, tobacco smoke, NO_2, fog, high humidity, SO_2, car exhaust, wood smoke
Respiratory Infections	Rhinovirus, respiratory syncytial virus, influenza, parainfluenza, *Mycoplasma pneumonia*, chlamydia
Emotions	Anxiety, stress
Exercise	Especially in cold, dry environments
Drugs	Beta-blockers, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs)
Occupational Substances	Sulfites and other preservatives, flour dust, wood by-products, hay mold, various chemicals

Clinical Presentation

The characteristic symptoms of asthma are episodes of breathlessness, wheezing, coughing, and dyspnea or chest tightness, ranging from mild to life-threatening. Wheezing is caused by airflow limitation, producing a high-pitched whistling sound, usually heard on expiration (but may also be heard on inspiration). It is thought that cough is caused by stimulation of sensory nerves in the airways by inflammatory mediators released by the inflammatory cells involved in asthma. Dyspnea or chest tightness is the sensation associated with the increased work necessary for breathing when the airways are constricted.[NHLBI EPR-3]

The NAEPP Expert Panel-3 recommends that the clinician trying to establish a diagnosis of asthma should determine if episodic symptoms of airflow obstruction are present, airflow obstruction is at least partially reversible, and if alternative diagnoses can be excluded. Specifically, they recommend that clinicians should consider a diagnosis of asthma and perform spirometry (spirometry is needed to establish a diagnosis of asthma) if any of these indicators are present (as the presence of multiple key indicators increases, the probability of a diagnosis of asthma increases):[NHLBI EPR-3]

- Wheezing
- History of any of the following:
  — Cough, worse particularly at night
  — Recurrent wheeze
  — Recurrent difficulty in breathing
  — Recurrent chest tightness
- Symptoms occur or worsen in the presence of:
  — Exercise
  — Viral infection
  — Animals with fur or hair
  — House-dust mites (in mattresses, pillows, upholstered furniture, carpets)
  — Mold
  — Smoke (tobacco, wood)
  — Pollen
  — Changes in weather
  — Strong emotional expression (laughing or crying hard)
  — Airborne chemicals or dusts
  — Menstrual cycles
- Symptoms occur or worsen at night, awakening the patient.

The NAEPP classification of asthma severity uses measures in both the impairment and risk domains. This information can be used to guide decisions for therapy (see **Tables 1.2.2** and **1.2.5**).[NHLBI EPR-3]

Table 1.2.2: Classifying Asthma Severity in Persons ≥ 12 Years of Age and Not Currently Taking Long-term Control Medications.*NHLBI EPR-3

Components of Severity		Classification of Asthma Severity ≥12 years of age			
				Persistent	
		Intermittent	Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8 - 19 yr 85% 20 - 39 yr 80% 40 - 59 yr 75% 60 - 80 yr 70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3-4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1x on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced > 5%
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year (see note)	>2/year (see note) →		
		← Consider severity and interval since last exacerbation. → Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Treatment (See "Stepwise Approach for Managing Asthma" for treatment steps.)		Step 1	Step 2	Step 3	Step 4 or 5 and consider short course of oral systemic corticosteriods
		In 2-6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2-4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absense of impairment levels consistent with presistent asthma.

**The level of severity is determined by assessment of both impairment and risk. The impairment domain is assessed by the patient's/caregiver's recall of the previous 2-4 weeks and spirometry. Severity is assigned to the most severe category in which any feature occurs. At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.*[NHLBI EPR-3]

Societal and/or Economic Impact

In 2007, it is estimated that the total direct and indirect costs for asthma amounted to $19.7 billion: direct and indirect medical expenditures accounted for $14.7 billion and $5.0 billion, respectively. The single largest expenditure ($6.2 billion) is for prescription drugs, followed by hospitalizations ($4.7 billion).[ALA 2007]

In 2005, there were 15.9 million outpatient asthma visits to physician offices, hospital outpatient departments, and emergency departments.[ALA 2007]

There were 489,000 asthma hospitalizations in 2005, or 16.6 per 10,000 people. Females had a higher rate of hospitalization compared to males (19.7 per 10,000 compared to 13.3 per 10,000. Among children 0-14 years, there were 159,302 hospitalizations (26.2 per 10,000). Hospitalizations were highest among patients 65 years of age and older, 30.5 hospitalizations per 10,000. The asthma hospitalization rate for blacks was higher than for whites (27.0 per 10,000 compared to 11.1 per 10,000, respectively).[ALA 2007]

Asthma attacks interfere with daily activities, including attending school and going to work. Table 1.2.3 shows school and work days missed due to asthma among those who reported at least one asthma attack in 2003. There is no data for the number of days of work missed by an adult caring for an asthmatic child.

Table 1.2.3: Days Missed Due to Asthma Among Those Who Reported at Least One Asthma Attack in the Previous Year: United States, 2003[ALA 2007]

Days missed 2002 2003	**2003**
School days, children 5-17 years	12.8 million
Work days, currently employed adults 18 years and over	10.1 million

The important economical impact of the use of inhaled corticosteroids as maintenance therapy in patients with asthma has been evaluated. A retrospective review of the direct costs associated with patients with mild persistent asthma in relation to the pattern of inhaled corticosteroid use was performed using the administrative claims submitted for the employees, spouses, and dependents of 17 large self-insured U.S. companies. Patients were identified if they had at least one asthma diagnosis noted in their medical claims between January 1, 2001 and June 30, 2002, did not have a diagnosis for chronic obstructive pulmonary disorder, were younger than 65 years of age, and met other various criteria for the period of July 1, 2002 to June 30, 2003 (see publication). Asthma severity was based on GINA guideline recommendations and the use of medications over a 12-month period. Inhaled corticosteroid (ICS) use was determined using claims history (no/low usage- 0 to 2 claims per evaluation time period, consistent usage- 3 or more claims per evaluation time period). Direct asthma-specific medical costs were based on claims filed during the evaluation time period. Medication cost and payments for medical services were included in the analysis but patient out-of-pocket costs were not

included. This cost evaluation included inhaled corticosteroids other than ciclesonide due to the fact that it was not available in the U.S. at that time. Data regarding the cost evaluation of ciclesonide are not available at this time.[Colice]

Results

Direct healthcare costs were higher for patients with no/low ICS usage ($4,952) compared to consistent ICS usage ($3,747, $p<0.05$). The excess medical cost was due mostly to increased hospital costs in the no/low ICS usage group. Asthma-specific healthcare cost was higher in patients with no/low ICS use ($1,332) compared to consistent ICS use ($789, $p<0.01$). Asthma-specific drug cost for both groups was similar (no/low ICS- $552 vs. consistent ICS- $591, $p>0.05$).[Colice]

Approaches to Treatment

The goals for successful management of asthma outlined in the 2007 US National Heart, Lung, and Blood Institute (NHLBI) publication "Global Strategy for Asthma Management and Prevention" include the following:[NHLBI EPR-3]

Reduce Impairment:

- Prevent chronic and troublesone symptoms (e.g. coughing or breathlessness in the daytime, in the night, or after exertion).
- Require infrequent use (≤2 days a week) of inhaled SABA for quick relief of symptoms (not including prevention of exercise-induced bronchospasm (EIB).
- Maintain (near) normal pulmonary function.
- Maintain normal activity levels (including exercise and other physical activity and attendance at school or work).
- Meet patients' and families' expectations of and satisfaction with asthma care.

Reduce Risk:

- Prevent recurrent exacerbations of asthma and minimize the need for ED visits of hospitalizations.
- Prevent loss of lung function; for children, prevent reduced lung growth.
- Provide optimal pharmacotherapy with minimal or no adverse effects of therapy.

It is recommended that the reader consult the full NHLBI Guidelines for details; however, the following is a summary of the assessment and related treatments recommended in the NHLBI Guidelines.

The Key points as stated in the Guidelines are:

- The main goals of asthma treatment are to reduce impairment and reduce risk.
- Treatment should include patient education, control of environmental factors, and medications.[NHLBI EPR-3]

Assessing and monitoring asthma control NHLBI EPR-3

- Use severity classification chart, assessing both domains of impairment and risk, to determine initial treatment.
- Use asthma control chart, assessing both domains of impairment and risk, to determine if therapy should be maintained or adjusted (step-up if necessary, step-down if possible, see **Table 1.2.4 and 1.2.5**).
- Use multiple measures of impairment and risk: different measures assess different manifestations of asthma, they may not correlate with each other and they may respond differently to therapy. Obtain lung function measures by spirometry at least every 1-2 years, more frequently for not well-controlled asthma.
- Asthma is highly variable over time, and periodic monitoring is essential. In general, consider scheduling patient at 2- to 8-week intervals while gaining control; at 1-6 month intervals, depending on step of care required or duration of control, to monitor if sufficient control is maintained; at 3 month intervals if a step-down in therapy is anticipated.
- Assess asthma control, modification technique, written asthma action plan, patient adherence, and concerns at every visit.

Treatment Steps for Achieving Control NHLBI EPR-3

Most of the medications available for asthma patients, when compared with medications used for other chronic diseases, have extremely favorable therapeutic ratios. In general, since inhaled corticosteroids (ICS) work on the underlying inflammation resulting in a patient's asthma, these agents are the preferred maintenance treatment for asthma. In addition to ICS medications, others including antileukotrienes/leukotriene receptor antagonists (including zileuton and monteleukast) and long-acting $beta_2$-agonists (including salmeterol and formoterol) are utilized as maintenance treatments for asthma.

Each step represents treatment options that are alternatives for controlling asthma. Steps 1 to 5 provide options of increasing efficacy, except for Step 5 where issues of availability and safety influence the selection of treatment. Step 2 is the initial treatment for most treatment-naive patients with persistent asthma symptoms. If symptoms at the initial consultation suggest that asthma is severely uncontrolled (**Table 1.2.4**), treatment should be commenced at Step 3.

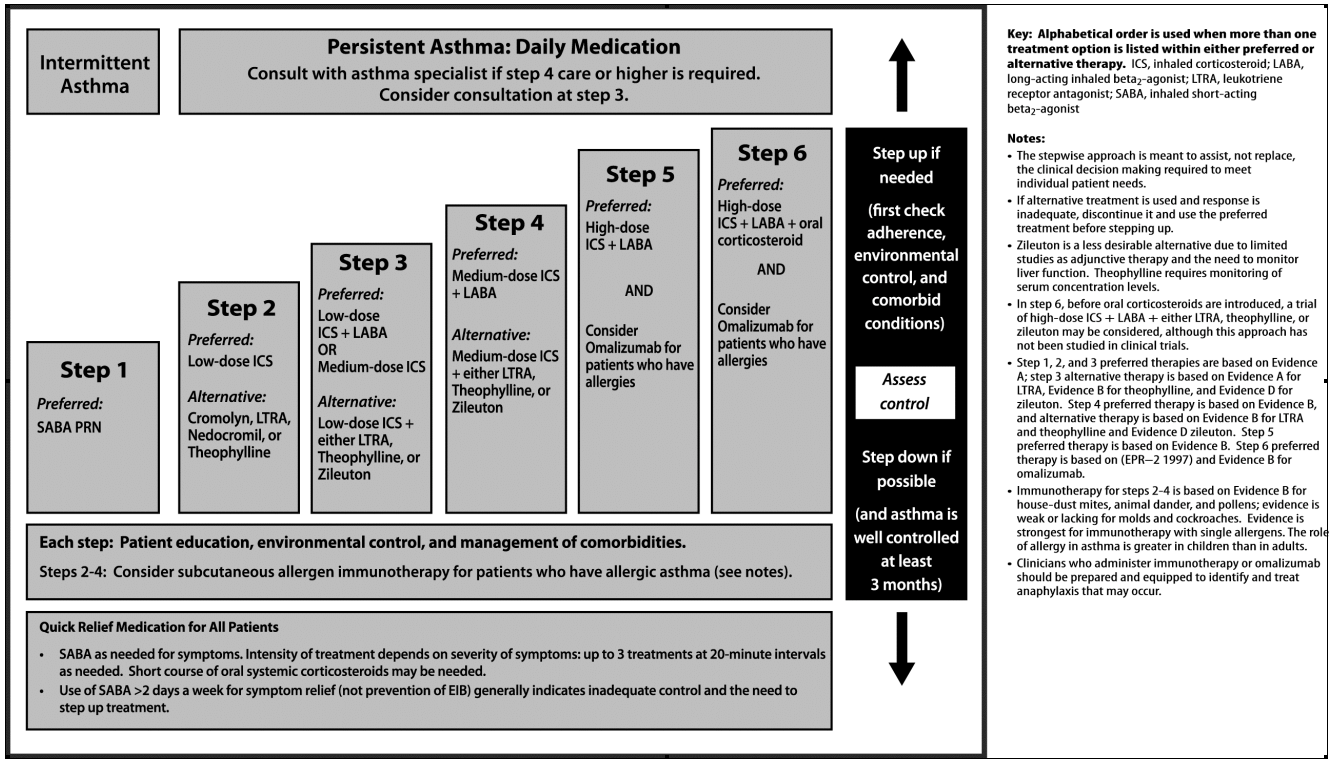
At each treatment step, a reliever medication (**rapid-onset bronchodilator)** should be provided for quick relief of symptoms. However, regular use of reliever medication is one of the elements defining uncontrolled asthma and indicates that controller treatment should be increased. Thus, reducing or eliminating the need for reliever treatment is both an important goal and a measure of success of treatment. For Steps 2 through 5, a variety of controller medications are available.

Table 1.2.4: Assessing Levels of Asthma Control in Adults and Adolescents 12 Years of Age and Older Currently Taking Long-term Control Medications NHLBI EPR-3

Characteristic	Well Controlled (All of the following)	Not Well Controlled (Any measure present in any week)	Very Poorly Controlled
Daytime symptoms	No more than 2 days/week	More than 2 days/week	Throughout the day
Limitations of activities	None	Some limitation	Extremely limited
Nocturnal symptoms/awakening	Less than 2 times in one month	1-3 times in one week	4 or more times a week
Need for reliever/ rescue treatment	Twice or less/week	More than twice/week	Several times a day
Lung function (PEF or FEV_1)‡	>80% predicted or personal best	≥60% and ≤80% predicted or personal best	< 60% predicted or personal best
Exacerbations	0-1 per year	Two or more a year*	Two or more a year*

* *Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate.*
† *By definition, an exacerbation in any week makes that an uncontrolled asthma week.*
‡ *Lung function is not a reliable test for children 5 years and younger.*

Table 1.2.5: Stepwise Approach for Managing Asthma in Youths ≥ 12 Years of Age and Adults From the NAEPP Expert Panel Report-3, 2007[NHLBI EPR-3]



Key: Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy. ICS, inhaled corticosteroid; LABA, long-acting inhaled beta$_2$-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Zileuton is a less desirable alternative due to limited studies as adjunctive therapy and the need to monitor liver function. Theophylline requires monitoring of serum concentration levels.
- In step 6, before oral corticosteroids are introduced, a trial of high-dose ICS + LABA + either LTRA, theophylline, or zileuton may be considered, although this approach has not been studied in clinical trials.
- Step 1, 2, and 3 preferred therapies are based on Evidence A; step 3 alternative therapy is based on Evidence A for LTRA, Evidence B for theophylline, and Evidence D for zileuton. Step 4 preferred therapy is based on Evidence B, and alternative therapy is based on Evidence B for LTRA and theophylline and Evidence D zileuton. Step 5 preferred therapy is based on Evidence B. Step 6 preferred therapy is based on (EPR—2 1997) and Evidence B for omalizumab.
- Immunotherapy for steps 2-4 is based on Evidence B for house-dust mites, animal dander, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults.
- Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.

One of the challenges of using an inhaled corticosteroid for the maintenance treatment of asthma is patient compliance. Compliance can be affected by the fact that an inhaled corticosteroid provides long-term control of symptoms rather than immediate symptom relief. Another factor that can contribute to compliance is the incidence of adverse events. It is important for the healthcare provider to consider the adverse events occurring in the patient that they are treating and how it will affect compliance. The following is a summary of a review that evaluated the effect of various adverse events that commonly occur with inhaled corticosteroids on patient compliance.

The rates of adherence to inhaled corticosteroids and the relationship of adherence to adverse events experienced were evaluated in a retrospective review using patient surveys, medical claims, and pharmacy claims. Patients (6-64 years of age) with a diagnosis of persistent asthma and at least two pharmacy claims for an inhaled corticosteroid from January 01, 2000 to December 31, 2005 were included in the review. Adherence was based on the ratings in a patient survey (from 0 for high adherence to 4 for low adherence) over a 1 year period, excluding COPD surveys Local adverse events (LAE) were assessed both through medical records and patient surveys. Please note that this review did not include ciclesonide, as it was not yet commercially available in the U.S.[Ivanova]

Results

Adherence was rated as good (adherent defined as a medication possession rate of at least 80% according to medical and pharmacy claims) in 2.7% of patients using claim-based evaluation. Patient-reported adherence was rated as good in 20.7% of patients. Local adverse events were reported in 27.2% of the patients; 5.6% of patients had at least one LAE related to ICS. The most common adverse local events reported were pharyngitis, throat pain, and hoarseness. Of the patients that reported local adverse events, the majority of patients reported minimal hoarseness (52.4%) or bad taste (65.3%); only 21.8% patients reported oral thrush. Of those patients experiencing local adverse events, 47% were bothered "quite a lot" by at least one local side-effect. Patients with low adherence were more often affected by voice problems, unpleasant taste, and itching in the mouth compared to high adherence patients. Unpleasant taste and itching in the mouth were also more commonly experienced in patients with medium adherence than in high adherence patients. Analysis indicated that only unpleasant taste was statistically related to low adherence.[Ivanova]

Description of Alternative Treatment Options

The non-pharmacological aspects of therapy incorporated into the NHLBI stepwise approach to treatment include patient education and building patient self-management skills, use of peak-flow meters for persons with moderate and severe persistent asthma, allergen avoidance in patients with known allergic triggers for their asthma, and smoking cessation for patients who smoke as well as parents of children with asthma. Treatment plans should include elements to promote self-management.

Place of ALVESCO in Treatment

ALVESCO is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and adolescent patients 12 years of age and older. Based on the available treatment guidelines for asthma, ALVESCO can be used in adult patients with persistent asthma. The results from clinical trials performed with ALVESCO demonstrated that ALVESCO is effective in improving pulmonary functioning, while resulting in an adverse event profile similar to placebo. As a result of its efficacy and safety profile, ALVESCO can be a viable alternative to other ICSs currently used in the maintenance and prophylactic treatment of persistent asthma in patients 12 years of age and older.

Relevant Treatment Guidelines

In 2007, The National Asthma Education and Prevention Program (NAEPP) has issued clinical guidelines through the National Heart, Lung, and Blood Institute for the diagnosis and management of asthma and provides guidance for selecting treatment based on a patient's individual needs and level of asthma control. The NHLBI guidelines can be found at the following link:
http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.

In addition, recently updated asthma treatment guidelines are available from the Global Initiative for Asthma (GINA), National Heart, Lung and Blood Institute (2007) at:
www.Ginasthma.com/guidelineitem.asp??l1=2&l2=1&int1d=60.

1.3 Evidence for Pharmacogenomic Tests and Drugs

Asthma has an inheritable component, however, the genetics of asthma continue to be evaluated. As the implication of having various phenotypes of asthma becomes clearer, treatment approaches may be chosen or avoided depending on specific genotype and phenotype. No formal consensus has been made at this point in time.[NHLBI EPR-3]

2. Supporting Clinical and Economic Information

2.1 Overview of Key Clinical Efficacy and Safety Studies

ALVESCO Inhalation Aerosol is an inhaled corticosteroid indicated for the maintenance treatment of asthma as prophylactic therapy to be administered twice a day in adult and adolescent patients 12 years of age and older. ALVESCO is NOT U.S. approved for once-daily use, the relief of acute bronchospasm, or for use in children under 12 years of age.

For complete Safety information, please refer to the enclosed Prescribing Information.

The recommended starting dose and the highest recommended dose of ALVESCO Inhalation Aerosol are listed in **Table 2.1.1** below:

Table 2.1.1: Recommended Dosages of ALVESCO Inhalation Aerosol in Adults and Adolescents ≥ 12 Years of Age[PI]

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Receiving Bronchodilators Alone	80 mcg twice daily	160 mcg twice daily
Receiving Inhaled Corticosteroids	80 mcg twice daily	320 mcg twice daily
Receiving Oral Corticosteroids*	320 mcg twice daily	320 mcg twice daily

*Prednisone should be reduced gradually, no faster than 2.5 mg/day on a weekly basis, beginning after at least 1 week of therapy with ALVESCO. Patients should be carefully monitored for signs of asthma instability, including monitoring of serial objective measures of airflow, and for signs of adrenal insufficiency during steroid taper and following discontinuation of oral corticosteroid therapy [see **Warnings and Precautions** in enclosed package insert].

Some of the information contained within this section of the dossier is not contained in the FDA-approved prescribing information for ALVESCO, and is being included within this dossier in order to provide the reviewer with a complete overview of representative data available for ALVESCO (per the AMCP guidelines for dossiers). Reference citations for other published material not fully described within this dossier are also provided. Note the references cited are not meant to be all-inclusive. Additionally, please refer to the enclosed prescribing information for complete prescribing and safety information.

The FDA evaluated the efficacy of six clinical trials (see **Table 2.1.2**) for U.S. approval.[DOF 3031, 3030, M1-323/324, M1-325, Bateman 2006, M1-321,322] In these trials, approximately, 800 patients 12 years of age and older received ciclesonide inhalation aerosol 80 mcg, 160 mcg, or 320 mcg twice daily. **The results of these trials indicate that twice-daily dosing is effective and once-daily dosing is not the optimum dosing regimen for ALVESCO.**

Additional trials comparing twice-daily (see **Table 2.1.3**) or once-daily (see **Table 2.1.4**) administration of ciclesonide inhalation aerosol to other corticosteroids have been performed. Other trials evaluating ciclesonide inhalation aerosol in pediatric patients 4 to 11 years of age (See **Table 2.1.5)** are listed and described in the following section.

Table 2.1.2: U.S. FDA Approval:
Efficacy and Safety Trials in Adults and Adolescents 12 Years of Age and Older

Study Number(s) (Publication)	Population (N)	Treatment Duration	Treatment Arms*
3031	N=691 Mild to moderate asthma Previously maintained on bronchodilators	16 weeks	CIC 80 mcg BID CIC 160 mcg QD_{AM} CIC 80 mcg BID→CIC 160 mcg QD_{AM} Placebo
3030	N=456 Mild to moderate asthma Previously maintained on inhaled corticosteroids	12 weeks	CIC 80 mcg BID CIC 160 mcg QD_{AM} Placebo
323/324	N=531 Moderate to severe asthma	12 weeks	CIC 160 mcg BID CIC 320 mcg BID FP 440 mcg BID CFC MDI Placebo
325 (Bateman 2006)	N=141 Severe persistent asthma Oral corticosteroid dependent	12 weeks	CIC 320 mcg BID CIC 640 mcg BID Placebo
323/324 LT	N=297 Severe persistent asthma	52 weeks	CIC 160 mcg BID CIC 320 mcg BID BDP 160 mcg BID HFA MDI BDP 320 mcg BID HFA MDI
321 (Pearlman 2005)**	N=526 Mild to moderate asthma	12 weeks	CIC 80 mcg QD_{AM} CIC 160 mcg QD_{AM} CIC 320 mcg QD_{AM} Placebo
322 (Pearlman 2005)**	N=489 Mild to moderate asthma	12 weeks	CIC 80 mcg QD_{AM} CIC 160 mcg QD_{AM} CIC 320 mcg QD_{AM} Placebo

* CIC denotes ciclesonide inhalation aerosol; FP, fluticasone propionate; BDP, beclomethasone dipropionate; HFA hydrofluoroalkane; MDI metered-dose inhaler. All doses are ex-actuator unless otherwise specified.
**Study 321 and 322 published as pooled data

Table 2.1.3: Twice Daily Comparator Trials: Adults and Adolescents 12 Years of Age and Older

Study number(s) (Publication)	Population (N)	Treatment Duration	Treatment Arms
103/2005 Bateman 2008	N=528 Moderate to severe persistent asthma	6 months	CIC 320 mcg BID FP 330 mcg BID HFA MDI
103 Szefler 2005	N=60 Moderate to severe asthma	4 weeks	CIC 320 mcg BID CIC 640 mcg BID FP 440 mcg BID CFC MDI FP 880 mcg BID CFC MDI Placebo
184/2004 Adachi 2007	N=319 Moderate to severe asthma	8 weeks	CIC 320 mcg QD_{PM} CIC 320 mcg BID BDP 400 mcg BID CFC MDI(ex-valve)
3027	N=1568 Moderate to severe asthma	12 months	CIC 320 mcg BID BDP 320 mcg BID HFA MDI

* CIC denotes ciclesonide inhalation aerosol; FP, fluticasone propionate; BDP, beclomethasone dipropionate; HFA hydrofluoroalkane; MDI metered-dose inhaler; CFC chlorofluorocarbon. All doses are ex-actuator unless otherwise specified.

Table 2.1.4: Once-Daily Comparator Trials: Adults and Adolescents 12 Years of Age and Older

Study number(s) (Publication)	Population (N)	Treatment Duration	Treatment Arms
369/2003 Magnussen 2007	N=1045 Persistent asthma	12 weeks	CIC 80 mcg QD_{PM} CIC 160 mcg QD_{PM} FP 88 mcg BID MDI
196/2002 Buhl 2006	N=529 Persistent asthma	12 weeks	CIC 160 mcg QD_{PM} FP 88 mcg BID HFA MDI
193/2000 Hansel 2006	N=554 Mild to moderate asthma	12 weeks	CIC 80 mcg QD_{AM} CIC 320 mcg QD_{AM} BUD 200 mcg BID DPI
88/2003 Niphadkar 2005	Persistent asthma	12 weeks	CIC 160 mcg QD_{AM} or QD_{PM} BUD 200 mcg BID (ex-valve) HFA MDI
59/2005 Vermeulen 2007	N=431 Severe Asthma	12 weeks	CIC 320 mcg QD_{PM} BUD 800 mcg BID DPI

* CIC denotes ciclesonide inhalation aerosol; FP, fluticasone propionate; BDP, beclomethasone dipropionate; BUD, budesonide; HFA hydrofluoroalkane; MDI metered-dose inhaler; DPI dry powder inhaler. All doses are ex-actuator unless otherwise specified.

Table 2.1.5: Pediatric Trials, Ages 4-11

Study Number(s) (Publication)	Population (N)	Treatment Duration	Treatment Arms*
341 Gelfand 2006**	N=514 Persistent asthma	12 weeks	CIC 40 mcg QD_{AM} CIC 80 mcg QD_{AM} CIC 180 mcg QD_{AM} Placebo
342 Gelfand 2006**	N=517 Persistent asthma	12 weeks	CIC 40 mcg QD_{AM} CIC 80 mcg QD_{AM} CIC 180 mcg QD_{AM} Placebo
341 LT	N=193 Mild to severe persistent asthma	1 year	CIC 40 mcg QD_{AM} CIC 80 mcg QD_{AM} CIC 160 mcg QD_{AM} FP 50 mcg BID (ex-valve) DPI FP 100 mcg BID (ex-valve) DPI Placebo
342 LT	N=190 Mild to severe persistent asthma	1 year	CIC 40 mcg QD_{AM} CIC 80 mcg QD_{AM} CIC 160 mcg QD_{AM} FP 50 mcg BID (ex-valve) DPI FP 100 mcg BID (ex-valve) DPI Placebo
343 Skoner 2008	N=661 Mild persistent asthma	1 year	CIC 40 mcg QD_{AM} CIC 160 mcg QD_{AM} Placebo
54/2003 Pedersen 2006	N=556 Persistent asthma	12 weeks	CIC 80 mcg BID FP 88 mcg BID HFA MDI
278/2004 Von Berg 2007	N=621 Persistent asthma	12 weeks	CIC 160 mcg QD_{AM} BUD 400 mcg QD_{PM} DPI

* CIC denotes ciclesonide inhalation aerosol; FP,fluticasone propionate; BUD, denotes budesonide; HFA hydrofluoroalkane; MDI metered-dose inhaler. All doses are ex-actuator unless otherwise specified.

** Identical trials 341/342 results presented in single publication as pooled data (Gelfand 2006)

*** Pediatric trial recently completed. Data compilation ongoing.

2.2 Key Clinical and Economic Studies

U.S. FDA Approval: Efficacy and Safety Trials

Adults and Adolescents (12 and Older)-12 to 16 weeks Duration

Mild to Moderate Persistent Asthma-Patients Maintained on Bronchodilators Alone

Efficacy and safety of ciclesonide metered-dose inhaler in adults and adolescents with mild to moderate persistent asthma not treated with steroids. Data on File. Clinical Study Report 3031; Marlborough, Mass: Sepracor Inc.

Objective:
Investigate the efficacy and safety of ciclesonide, compared to placebo, administered for 16 weeks in a once-daily regimen in the morning (160 mcg QD_{AM}), in a twice-daily regimen (80 mcg BID), or in a cross-over regimen of 160 mcg QD_{AM} for 4 weeks followed by 80 mcg BID for 8 weeks in adults and adolescents with mild to moderate asthma who were previously maintained on bronchodilators.

Study Design and Population:
This Phase III, randomized, double-blind, parallel-group, placebo-controlled, 16-week trial was performed at 139 centers in 11 different countries, including the U.S. The trial evaluated the efficacy of three dosing regimens of ciclesonide inhalation aerosol MDI [160 mcg QD_{AM} (n = 178), 80 mcg BID (n = 175), and 80 mcg BID for four weeks followed by 160 mcg QD_{AM} for 12 weeks (n = 177]) compared to placebo (n = 178) in patients 12 years of age or older with a history of persistent bronchial asthma for at least 6 months prior to screening. An FEV_1 of between 60% and 85% of predicted normal after a 6-hour period with no albuterol treatment was required for inclusion in the trial. Patients were included if their asthma therapy consisted exclusively of bronchodilators for the month prior to screening.

The primary efficacy endpoint was AM pre-dose FEV_1. Key secondary endpoint variables included the morning peak expiratory flow, albuterol use, and total asthma symptom score. Treatment-emergent adverse events were monitored throughout the trial.

Results:
Patients were between 11 and 73 years of age with a median age range of 35 to 39 years. The mean FEV_1 percent predicted at baseline was 72.0%.

Table 2.2.1 below provides an overview of the treatment differences compared to placebo in the primary and key secondary endpoints from baseline to endpoint.

Table 2.2.1: Summary of Treatment Differences of Ciclesonide MDI Versus Placebo MDI-ITT Population from Baseline to Endpoint

Variable	Treatment difference versus placebo MDI [LS mean (95% CI) p-value]		
	Cic MDI 160 µg q.d. AM	Cic MDI 80 µg b.i.d./ 160 µg q.d. AM	Cic MDI 80 µg b.i.d.
Primary efficacy endpoint: Change from baseline to the average of Weeks 12 and 16			
FEV_1 (L)	0.12 (0.05; 0.20) 0.0021	0.13 (0.05; 0.20) 0.0016	0.24 (0.16; 0.32) <0.0001
Key secondary efficacy endpoints: Change from baseline to Week 16 (LOCF)			
AM PEF (L/min)	23.32 (10.08; 36.53) 0.0006	30.71 (17.70; 43.71) <0.0001	36.16 (23.13; 49.20) <0.0001
Albuterol use (puffs/day)	-0.41 (-0.73; -0.09) 0.0116	-0.60 (-0.92; -0.28) 0.0002	-0.73 (-1.04; -0.41) <0.0001
Total asthma symptom score (0-8 scale)	-0.27 (-0.57; 0.03) 0.0781	-0.32 (-0.62; -0.03) 0.0325	-0.57 (-0.87; -0.27) 0.0002

Cic = ciclesonide; LS = least squares; CI = confidence interval; MDI = metered-dose inhaler; b.i.d. = twice daily; q.d. = once daily; ITT = intent-to-treat

All three doses of CIC showed statistically significant improvements compared to placebo in terms of change in AM pre-dose FEV_1 from baseline to the average of Weeks 12 and 16 (see **Figure 2.2.1**). All doses showed statistically significant improvements compared to placebo in change from baseline to Week 16 in AM PEF and albuterol use. For the total asthma symptom score, the treatment difference between CIC 160 mcg QD_{AM} group and placebo was not statistically significant.

Figure 2.2.1: Change in FEV_1 (L)

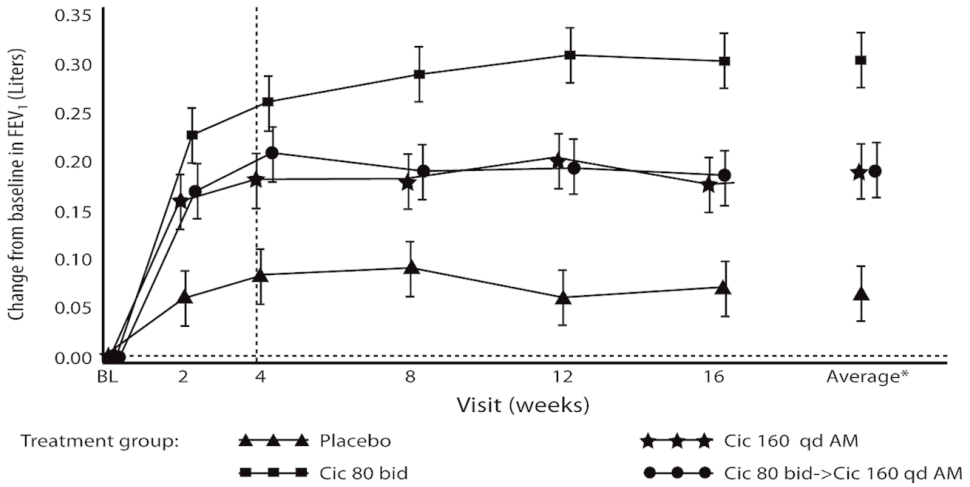


Figure presents LS means ± SE.
BL = baseline; FEV1 = forced expiratory volume in 1 second; LOCF = last observation carried forward; Cic = ciclesonide; qd AM = once daily in the morning; bid = twice daily
* = average of Weeks 12 and 16.
At all visits, the p-values were <0.005 for the treatment comparisons of each of the ciclesonide MDI groups versus placebo MDI.

The percentage of patients experiencing treatment-emergent adverse events was comparable among treatment groups (BID- 55.5%, QD- 52.8%, BID to QD- 57.8%, and placebo- 57.3%). The most common adverse events occurring in at least 3% of patients for BID, QD, BID to QD, and placebo groups were asthma 5.2%, 8.0%, 10.4% and 14%; nasopharyngitis 11.6%, 10.8%, 5.2% and 9.6%; headache 5.8%, 9.1%, 8.7% and 7.9%; upper respiratory tract infection 5.2%, 3.4%, 7.5% and 6.2%; influenza 3.5%, 4.5%, 3.5% and 1.7%; pharyngolaryngeal pain 2.9%, 2.8%, 2.3% and 4.5%; back pain 0.6%, 1.1%, 3.5% and 1.7%; and sinusitis 2.9%, 4.0%, 3.5% and 1.7%. A higher percentage of patients permanently discontinued study medication due to a treatment-emergent adverse event in the placebo group (12.4%) compared to the CIC QD, BID to QD, and BID groups (8.0%, 4.6%, and 2.3%).

The incidence of oropharyngeal adverse events was similar between the treatment groups (for BID, QD, BID to QD, and placebo groups: pharyngolaryngeal pain 2.9%, 2.8%, 2.3% and 4.5%; pharyngitis 2.9%, 0.6%, 1.7%, and 0.6%; and dysphonia 0%, 0.6%, 0%, and 0.6%). There were no cases of oral candidiasis.

Conclusion:

In this trial ciclesonide was effective compared to placebo in patients with mild to moderate asthma previously treated with inhaled bronchodilators alone and was well-tolerated compared to placebo.

Mild to Moderate Persistent Asthma-Patients Maintained on Inhaled Corticosteroids

Efficacy and safety of ciclesonide metered-dose inhaler in adults and adolescents with mild to moderate persistent asthma treated previously with inhaled steroids. Data on File. Clinical Study Report 3030.

Objective:
Investigate the efficacy and safety of ciclesonide, compared to placebo, at a daily dose of 160 mcg administered for 12 weeks in a once-daily regimen in the morning (160 mcg QD_{AM}) or in a twice-daily regimen (80 mcg BID) in adults and adolescents with mild to moderate asthma who were previously maintained on inhaled corticosteroids.

Study Design and Population:
A Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial was performed in adults and adolescents with mild to moderate persistent asthma previously maintained on inhaled corticosteroids to assess the efficacy and safety of a once daily dose of ciclesonide or a twice a day dose of ciclesonide compared to placebo. Thirty-eight centers throughout the U.S. participated in the trial. Patients 12 years of age and older were randomized to receive ciclesonide inhalation aerosol MDI 160 mcg QD_{AM} (n = 152), ciclesonide 80 mcg BID (n = 152), or placebo (n = 152) for 12 weeks. Patients had at least a six month history of persistent asthma treated with either an inhaled corticosteroid (ICS, $\leq$ 440 mcg/day of fluticasone or equivalent) or an inhaled corticosteroid/long-acting beta-agonist combination (ICS/LABA, $\leq$ 200/100 mcg/day of fluticasone propionate/salmeterol) during the month prior to screening. Patients continued their treatments during the 7- to 14-day screening period. At randomization, patients discontinued their current therapy were included if their FEV_1 was 60%-90% of predicted normal if maintained on ICS or 70%-95% of predicted normal if maintained on ICS/LABA therapy.

The primary efficacy endpoint was AM pre-dose FEV_1. Key secondary endpoint variables included the morning peak expiratory flow, albuterol use, and total asthma symptom score. Treatment-emergent adverse events were monitored throughout the trial.

Results:
Patients were between 12 and 79 years of age with a median age range of 37 to 44 years. The mean FEV_1 percent predicted at baseline was approximately 79%.

Table 2.2.2 below provides an overview of the treatment differences compared to placebo in the primary and secondary endpoints from baseline to the endpoint.

Table 2.2.2: Summary of Treatment Differences of Ciclesonide MDI Versus Placebo MDI-ITT Population from Baseline to Week 12

Variable	Treatment difference at Week 12 (LOCF) versus placebo MDI (LS mean [95% CI] *P* value)	
	Cic MDI 160 µg q.d. AM	Cic MDI 80 µg b.i.d.
Primary efficacy variable		
FEV_1 (L)	0.14 (0.06; 0.22) 0.0006	0.19 (0.11; 0.27) <0.0001
Key secondary efficacy variables		
AM PEF (L/min)	7.05 (-0.76; 14.86) 0.0769	8.39 (0.60; 16.19) 0.0349
Albuterol use (puffs/day)	-0.60 (-0.91; -0.28) 0.0002	-0.64 (-0.95; -0.33) <0.0001
Total asthma symptom score (0-8 scale)	-0.38 (-0.60; -0.15) 0.0010	-0.37 (-0.60; -0.15) 0.0011

Cic = ciclesonide; LS = least squares; CI = confidence interval

Both regimens of CIC improved the AM pre-dose FEV_1 from baseline to Week 12 significantly more than placebo (see **Figure 2.2.2**). Both regimens provided a significant decrease in albuterol use and improvements in asthma symptoms scores compared to placebo. Compared to the placebo group, there was statistically significant improvement in AM PEF for the CIC BID group but not for the CIC QD group. Overall, the secondary respiratory efficacy endpoints remained relatively stable for the ciclesonide treatment groups compared to a slight worsening in the placebo group.[PI]

Figure 2.2.2: Change in FEV_1 (L)

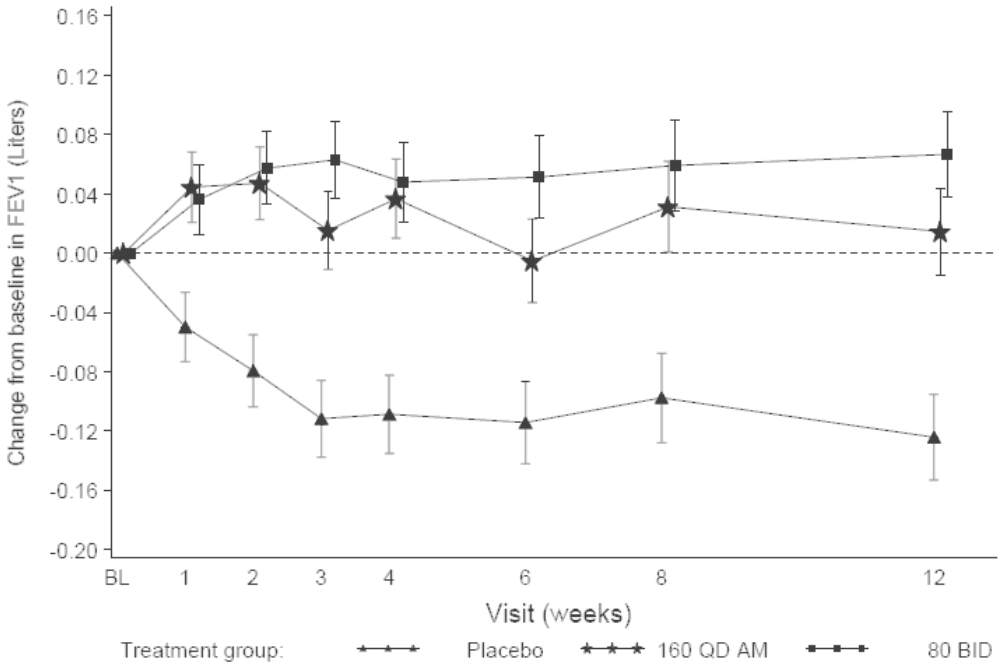


Figure presents LS means ± SE.
BL = baseline.
At all visits, the *P* values were <0.005 for the treatment comparisons of ciclesonide MDI 160 µg q.d. AM versus placebo MDI and ciclesonide MDI 80 µg b.i.d. versus placebo MDI.

The percentage of patients experiencing treatment-emergent adverse events for both treatment groups (52.0% of BID patients, and 57.9% of QD_{AM} patients) were comparable to placebo (55.3% of patients). A higher percentage of patients permanently discontinued study medication due to a treatment-emergent adverse event in the placebo group (15.8%) compared to the CIC QD_{AM} and BID groups (4.6% and 5.3%). The most common adverse events occurring in at least 2% of patients in either ciclesonide treatment group were nasopharyngitis (9.2%, 12.5% and 5.9% for BID, QD_{AM} and placebo), upper respiratory tract infection (9.2%, 7.9% and 7.9% for BID, QD_{AM} and placebo), pharyngolaryngeal pain (5.9%, 5.3% and 3.3% for BID, QD_{AM} and placebo), sinusitis (3.3%, 5.9% and 4.6% for BID, QD_{AM} and placebo), asthma (3.3%, 4.6% and 17.8% for BID, QD_{AM} and placebo), headache (3.9%, 3.9% and 3.9% for BID, QD_{AM} and placebo), cough (2.0%, 5.3% and 2.0% for BID, QD_{AM} and placebo), gastroenteritis viral (0.7%, 3.9% and 1.3% for BID, QD_{AM} and placebo), and toothache (0%, 3.3% and 1.3% for BID, QD_{AM} and placebo).

The incidence of oropharyngeal adverse events was similar among the treatment groups (for BID, QD_{AM}, and placebo groups: pharyngolaryngeal pain 5.9%, 5.3%, and 3.3%; pharyngitis 0%, 1.3%, and 0%; dysphonia 0%, 0% and 0.7%; and oral candidiasis 0.7%, 0%, and 0%).

Conclusion:

In this trial, ciclesonide administrated at a daily dose of 160 mcg as 80 mcg BID is effective compared to placebo in patients with mild to moderate asthma is effective. The data demonstrated that this dose was well-tolerated compared to placebo.

Moderate to Severe Persistent Asthma-Patients Maintained on Inhaled Corticosteroids

Efficacy and safety of ciclesonide metered-dose inhaler MDI and fluticasone MDI in adults and adolescents with moderate to severe persistent asthma treated previously with inhaled steroids. Data on File. Clinical Study Report 323/324.

Objective:
Compare the efficacy and safety of twice-daily administration of two dosing regimens of ciclesonide MDI, 160 mcg BID or 320 mcg BID, fluticasone propionate 440 mcg BID, or placebo in patients with moderate to severe persistent asthma previously maintained on inhaled corticosteroids.

Study Design and Population:
A Phase III, multicenter, randomized, double-blind, parallel-group, placebo-controlled and active-controlled trial of 12 weeks duration evaluated the efficacy and safety of ciclesonide inhalation aerosol in adults and adolescents 12 years of age or older with moderate to severe persistent asthma. Patients were enrolled from 87 sites throughout the U.S. Patients were required to have at least a one year history of persistent asthma, an FEV_1 of 80% or less of predicted normal following a six-hour beta-agonist treatment withholding period at screening, and an FEV_1 between 40% and 65% of predicted normal following a six-hour beta-agonist treatment withholding. Patients were included in the study if they had a documented use of ICS (≥ 500 mcg/day fluticasone or mometasone, or ≥ 800 mcg/day budesonide, beclomethasone, flunisolide, triamcinolone) and beta-agonist use of more than two times a week for the month prior to screening. Patients (n = 531) were randomized to receive HFA MDI formulation of ciclesonide inhalation aerosol 160 mcg BID (n = 127), ciclesonide 320 mcg BID (n = 130), placebo (n = 136), or CFC MDI formulation of fluticasone propionate (FP) 440 mcg BID (n = 138) as an active comparator.

The primary efficacy endpoint was the change from baseline to Week 12 in AM pre-dose FEV_1 compared to placebo. Secondary endpoints included the morning peak expiratory flow, albuterol use, total asthma symptom score, and changes in the Asthma Quality of Life Questionnaire (AQLQ). Treatment-emergent adverse events were monitored throughout the trial.

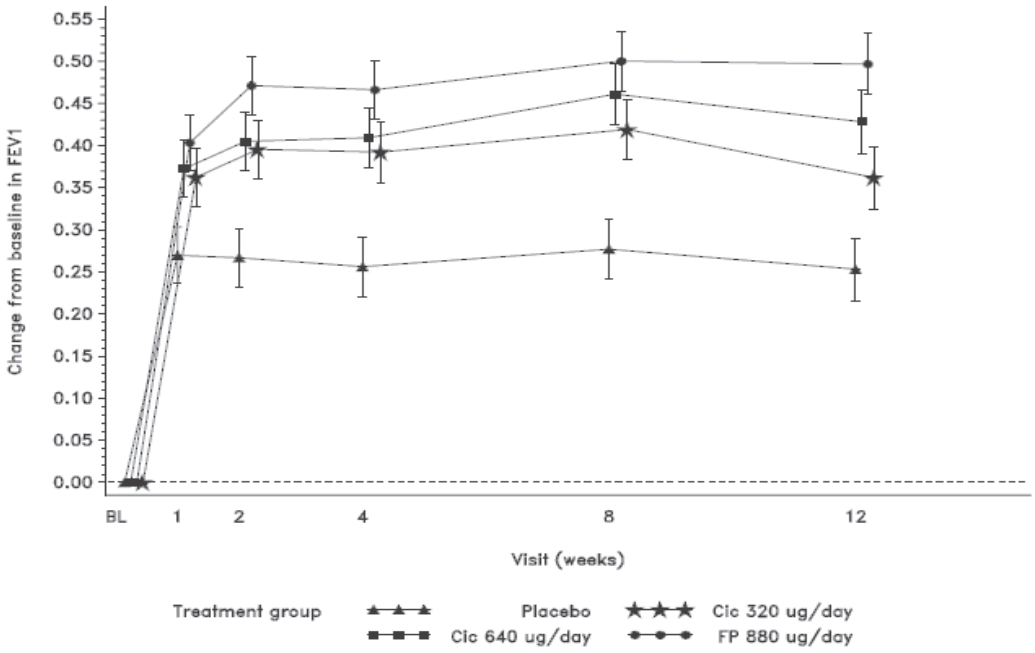
Results:
Patients were between 12 and 88 years of age with a mean age range of 42 to 44 years. The mean FEV_1 percent predicted at baseline was 53.7%. **Table 2.2.3** below provides an overview of treatment differences compared to placebo in the primary and key secondary endpoints from baseline to Week 12.

Figure 2.2.3: Summary of Treatment Differences of Ciclesonide MDI Versus Placebo MDI-ITT Population from Baseline to Week 12

	Treatment difference at Week 12 versus placebo LS mean (95% CI) p Value		
	CIC 160 mcg BID	**CIC 320 mcg BID**	**FP 440 mcg BID**
Primary efficacy variable FEV_1 (L)	0.11 (0.01, 0.21) 0.0374	0.18 (0.07, 0.28) 0.0008	0.24 (0.14, 0.35) 0.0001
Key secondary efficacy variables AM PEF (L/min)	27.80 (16.76,38.83) 0.0001	30.39 (19.49,41.30) 0.0001	41.42 (30.63,52.20) 0.0001
Albuterol use (puffs/day)	-1.69 (-2.35, -1.04) 0.0001	-1.57 (-2.22, -0.92) 0.0001	-2.19 (-2.84, -1.54) 0.0001
Total asthma symptom score (0-8 scale)	-0.71 (-1.05, -0.37) 0.0001	-0.80 (-1.14, -0.46) 0.0001	-0.91 (-1.24, -0.58) 0.0001

All active treatments showed an improvement in AM pre-dose FEV_1 from baseline to Week 12 compared to placebo (see **Figure 2.2.3**). Improvements in morning peak expiratory flow, albuterol use, and total asthma symptoms scores were significant in both of the ciclesonide treatment groups.

Figure 2.2.3: Change from Baseline Over 12 Weeks in FEV_1 (Liters)*



**Legend refers to daily mcg of ciclesonide and fluticasone (CIC 320 mcg/day refers to CIC 160 mcg BID, CIC 640 mcg/day refers to CIC 320 mcg BID, FP 880 mcg/day refers to FP 440 mcg BID)*

All four domains in the AQLQ (exposure to environmental stimuli, symptoms, activity limitation, and emotional function) were statistically significantly improved in both ciclesonide treatment groups and FP treatment group compared to placebo from baseline to Week 12. The percentage of patients who achieved the minimally important difference (MID) for improvement in the AQLQ Overall Score (an increase of at least 0.5) at Week 12 was 42.5% in the CIC 160 mcg BID group, 43.1% in the CIC 320 mcg BID group, and 58.8% in the FP treatment group compared with 26.9% in the placebo group.

The percentage of patients with treatment-emergent adverse events for all three of the active groups was comparable to the placebo group with treatment-emergent adverse events occurring in 61.4% of CIC 160 mcg BID patients, 54.6% of CIC 320 mcg BID patients, 60.1% of FP patients, and 61.8% of placebo patients. A higher percentage of patients permanently discontinued study medication in the placebo group (19.9%) compared to CIC 160 mcg BID, 320 mcg BID and FP treatment groups (6.3%, 7.7% and 4.3%). Treatment emergent adverse events reported by at least 10% of patients in any of the treatment groups (CIC 160 mcg BID, CIC 320 mcg BID, FP and placebo) included asthma aggravated (7.9%, 10.8%, 2.2% and 19.9%, respectively), nasopharyngitis (10.2%, 6.9%, 10.9% and 7.4%), and oral candidiasis (1.6%, 0%, 11.6% and 2.2%).

Oropharyngeal adverse events were more common in the FP group compared to the ciclesonide groups or placebo (for CIC 160 mcg BID, CIC 320 mcg BID, FP and placebo groups: oral candidiasis 1.6%, 0%, 11.6% and 2.2%; pharyngitis 4.7%, 3.1%, 5.1%, and 2.9%; and dysphonia 0%, 1.5%, 3.6%, and 0.7%).

Conclusion:

In this trial, daily doses of ciclesonide (160 mcg BID and 320 mcg BID) and fluticasone propionate (440 mcg BID) were effective compared to placebo in the treatment of adolescent and adult patients with moderate to severe persistent asthma. Findings support that 160 mcg BID and 320 mcg BID doses of ciclesonide are safe and effective for the maintenance treatment of moderate to severe persistent asthma as prophylactic therapy.

Severe Persistent Asthma- Patients Maintained on Oral Corticosteroids

Bateman E, Karpel J, Casale T, Wenzel S, Banerji D. Ciclesonide reduces the need for oral steroid use in adult patients with severe, persistent asthma. *CHEST*. 2006;129: 1176-1187. Clinical Study Report 325.

Objective:
Compare the oral steroid-sparing effects of ciclesonide MDI 320 mcg BID and 640 mcg BID to placebo in chronic oral corticosteroid-dependent patients with severe persistent asthma.

Study Design and Population:
A Phase III, multicenter, randomized, double-blinded, placebo-controlled, parallel-group trial evaluated the safety and efficacy of ciclesonide inhalation aerosol in patients with severe persistent asthma. This trial was performed in 60 sites located in the U.S. and South Africa. Eligible patients were those who had failed prior efforts to eliminate oral prednisone use and had established their lowest effective prednisone dose during the screening period. The patient s prednisone dose was decreased by an amount dependent on their maintenance dose at the first screening visit. The lowest effective prednisone dose was determined during subsequent FEV_1 and asthma symptom assessments during screening visits after the initial screening visit. Patients 12˚years of age and older were randomized to receive ciclesonide 320˚mcg BID (n = 47), ciclesonide 640˚mcg BID (n˚= 49), or placebo (n = 45) for 12˚weeks. Patients were required to have at least a one year history of persistent asthma, a regimen of oral corticosteroids (prednisone) at least every other day for five of the six months prior to screening and failure to completely eliminate oral prednisone, a history of inhaled corticosteroids during the six months prior to screening with a stable dose used the month immediately prior to screening, and the required use of an inhaled beta-agonist for asthma control within the two weeks prior to screening. Patients were included if their FEV_1 was between 40% and 80% of predicted normal after a 6-hour beta-agonist withholding period.

The primary efficacy endpoint was the percent change of oral prednisone dose from baseline to end of trial compared to placebo. Secondary endpoints included the percentage of patients who were able to completely discontinue prednisone use, changes in respiratory parameters (including percent change in baseline AM pre-dose FEV_1 and change in AM PEF), albuterol use, and total asthma symptom scores. An assessment of HPA-axis suppression was also evaluated. Treatment-emergent adverse events were monitored throughout the trial.

Results:
Patients were between 12 and 74 years of age with a median age of 48.3 years. The mean FEV_1 percent predicted at baseline was 53%. The average prednisone dose at baseline was approximately 12 mg/day.

As described in **Table 2.2.4** below, the percent reduction from baseline to the end of the trial (Week 12) in prednisone dose was 4.21% in placebo patients, indicating an increase in prednisone usage during the double-blind period. The percent reduction in prednisone

dose for the CIC 320 mcg BID group was -47.39% (p = 0.0003 vs. placebo) and for the CIC 640 mcg BID group was -62.54% (p = 0.0001 vs. placebo). Although the high-dose CIC group had a higher numerical percent reduction in prednisone dose than the low-dose CIC group, the differences were not statistically significant between the two ciclesonide treatment groups (p=0.274). The difference in the LS mean change in prednisone dose from baseline to Week 12 was statistically significantly greater in the CIC treatment groups compared to placebo. At Week 12, the percentage of patients that were able to completely discontinue oral prednisone usage was statistically significantly greater for patients in the CIC groups compared to the placebo group (see **Table 2.2.4**).

Table 2.2.4: Summary of Prednisone Reduction in Ciclesonide and Placebo Treatment Groups from Baseline to Week 12

Variable		Mean (p-value vs. placebo)		
		Placebo	Ciclesonide 640 µg/day	Ciclesonide 1280 µg/day
Percent reduction in prednisone dose	(%)	4.21	-47.39 (0.0003)	-62.54 (0.0001)
Percentage of patients eliminating prednisone usage	(%)	11.1	29.8 (0.0386)	31.3 (0.0233)
Change in prednisone dose	(mg/day)	0.72	-5.97 (0.0008)	-8.00 (0.0001)

Coincident with the reduction in prednisone dose, patients in the ciclesonide group maintained asthma control as evidenced by AM pre-dose $FEV_{1.}$ Differences in AM PEF, albuterol use, and asthma symptom scores were not significant in the treatment groups compared to the placebo group (see **Table 2.2.5**).

Table 2.2.5: Summary of Treatment Differences of Ciclesonide MDI Versus Placebo MDI-ITT Population from Baseline to Week 12

	Treatment difference at Week 12 versus placebo LS mean (95% CI) p Value	
	CIC 320 mcg BID	**CIC 640 mcg BID**
Key secondary efficacy variables FEV_1 (L)	0.17 (0.02, 0.31) 0.0237	0.17 (0.02, 0.31) 0.0277
AM PEF (L/min)	5.02 (-12.92, 22.96) 0.5803	16.67 (-1.62, 34.96) 0.0736
Albuterol use (puffs/day)	-0.39 (-1.80, 1.02) 0.5854	-0.40 (-1.83, 1.03) 0.5806
Total asthma symptom score (0-8 scale)	0.33 (-0.26, 0.92) 0.2669	-0.07 (-0.67, 0.53) 0.8197

A higher percentage of patients permanently discontinued study medication in the placebo group (26.7%) compared to the CIC 320 mcg BID and 640 mcg BID groups (14.9% and 8.2%).

The overall incidence of treatment-emergent adverse events were similar among the treatment groups (CIC 320 mcg BID: 85.1%, CIC 640 mcg BID: 79.6%, and placebo: 88.9%). The most common adverse events that occurred in 10% or more of patients in any treatment group (CIC 320 mcg BID, CIC 640 mcg BID, and placebo) were asthma aggravated (40.4%, 28.6%, and 62.2%), upper respiratory tract infection NOS (19.1%, 18.4%, and 20.0%), headache (14.9%, 12.2%, and 8.9%), sinusitis NOS (10.6%, 12.2%, and 4.4%), nasopharyngitis (6.4%, 12.2%, and 8.9%), arthralgia (0%, 14.3%, and 2.2%), vomiting NOS (0%, 4.1%, and 13.3%), oral candidiasis (see below), and pharyngitis (see below).

The incidence rates of oropharyngeal adverse events for the CIC 320 mcg BID, CIC 640 mcg BID and placebo groups were as follows: oral candidiasis- 6.4%, 12.2%, and 0%, dysphonia- 6.4%, 0%, and 2.2%, and pharyngitis- 6.4%, 4.1%, and 13.3%.

At baseline, 66.0% of patients in the ciclesonide 320 mcg BID group, 60.4% in the ciclesonide 640 mcg BID group, and 62.2% of patients in the placebo group had suppressed (non-normal) HPA-axis function. At Week 12, a smaller proportion of patients in both ciclesonide treatment groups had suppressed (non-normal) HPA-axis function compared with placebo (CIC 320 mcg BID- 46.8%; CIC 640 mcg BID- 43.8% and placebo- 53.3%).

Conclusion:
In this trial, in patients with severe persistent asthma who require oral corticosteroids for asthma control, ciclesonide in doses of 320 or 640 mcg given twice daily was an effective and safe alternative to oral corticosteroids. Ciclesonide may permit a reduction or complete elimination of the requirement for oral corticosteroids over time in comparison to placebo. **The highest recommended dose of ALVESCO Inhalation Aerosol is 320 mcg BID.**

Adults and Adolescents (12 and Older)-52 weeks Duration

Severe Persistent Asthma: Long-term evaluation

Long-term safety study of ciclesonide 160 mcg BID and 320 mcg BID in adult and adolescent patients with severe persistent asthma. Data on File. Clinical Study Report 323/324LT.

Objective:
Establish the long-term (12 month) safety of ciclesonide MDI 160 mcg BID and 320 mcg BID, as compared to beclomethasone HFA (QVAR®) MDI 160 mcg BID and 320 mcg BID in adults and adolescents with severe persistent asthma.

Study Design and Population:
A Phase III, multicenter, double-blind, randomized, one-year, long-term safety study was performed in patients with severe asthma. This was a 12-month extension of the 12-week pivotal trial previously described in patients with moderate to severe persistent asthma, previously maintained on inhaled corticosteroids (Study Report 323/324). Patients were enrolled from 63 sites throughout the U.S. To participate in the initial 12-week trial, patients were required to have at least a one year history of persistent asthma, an FEV_1 of 80% or less of predicted normal following a six-hour beta-agonist treatment withholding period at screening, and an FEV_1 between 40% and 65% of predicted normal following a six-hour beta-agonist treatment withholding period. Patients were included in the initial 12-week trial if they had a documented use of ICS (≥ 500 mcg/day fluticasone or mometasone, or ≥ 800 mcg/day budesonide, beclomethasone, flunisolide, triamcinolone) and beta-agonist use of more than two times a week for the month prior to screening. Patients who completed the original study or at least 2 weeks of the double-blind treatment were included for the extension. In addition, patients who had failed to qualify for the 12-week trial due to either a <10% drop in FEV_1 at Visit 3 (randomization) after a six-hour beta-agonist treatment withholding period compared to their FEV_1 at Visit 2 (screening) or an inability to tolerate discontinuation of their long-acting beta-agonist during the baseline period of the trial were eligible for inclusion in the long-term 12-month trial. Patients were randomized in a 2:1 ratio [HFA MDI ciclesonide to HFA MDI beclomethasone dipropionate (BDP)] to receive either CIC or BDP 320 mcg BID for the first two weeks of the trial. After two weeks, titration down to 160 mcg BID was allowed for either medication. Long-term safety data, the primary endpoint of the trial, was collected for patients receiving ciclesonide (n = 198) or BDP (n = 99).

Safety variables included adverse events, clinical laboratory values (including serum and urinary free cortisol), and physical examinations, including oropharyngeal and ophthalmologic. Although efficacy was not an endpoint for the trial, pulmonary parameters assessed were FEV_1, FEV_1 percent predicted, forced vital capacity (FVC) and forced mid-expiratory flow rate ($FEF_{25-75\%}$).

Results: Safety
Patients were between 12 and 76 years of age with a mean age range of 44.7 to 45.2 years of age. The mean FEV_1 percent predicted at baseline was 64.8%.

Frequency of treatment-emergent adverse events was comparable across treatment groups (CIC 74.1%, BDP 79.2%). The most common treatment-emergent adverse events reports (>10% of patients in any treatment group) were: asthma NOS (CIC 18.8%, BDP 18.8%), nasopharyngitis (CIC 14.2%, 19.8%), sinusitis (CIC 13.7%, BDP 6.3%), upper respiratory tract infection (CIC 11.2%, BDP 17.7%), headache (CIC 9.6%, BDP 15.6%), and oral candidiasis (see below).

The incidences of oropharyngeal adverse events were as follows: pharyngolaryngeal pain, CIC 3.0% and BDP 5.2%; oral candidiasis, CIC 4.1% and BDP 10.4%; pharyngitis, CIC 0.5% and BDP 0%; and dysphonia, CIC 2.5% and BDP 1.0%.

Lenticular opacities (cataracts) were reporterd in 9 patients at the end of study who had normal lenses at baseline: 6 patients (3.0%) received CIC, 2 patients (2.1%) received BDP, and one patient received both CIC and BDP. Glaucoma was reported in 2 patients treated with CIC and no patients treated with BDP. No occurrences of visual disturbance were reported in these patients or in the study population as a whole. There were no clinically meaningful adverse effects of CIC on HPA-axis or on any clinical laboratory analyte or vital sign.

Results: Efficacy

Significant improvements in FEV_1 were seen for both the CIC and BDP treatment groups from baseline to the end of study. The LS mean change in FEV_1 was 0.11 L for both treatment groups (95% CI for CIC 0.04, 0.18 and for BDP 0.02, 0.20).

Conclusion:

In this trial, the overall safety profile of ciclesonide and beclomethasone dipropionate HFA at doses up to 320 mcg twice-daily was comparable. The incidence of oral candidiasis was lower for ciclesonide compared to beclomethasone HFA. There were no meaningful differences between the active groups in HPA-axis function. These findings support the conclusion that ciclesonide at daily doses up to 320 mcg twice-daily are safe and effective for the maintenance treatment of severe persistent asthma as prophylactic therapy.

Other Twice-daily Non-comparator Trials:

The following table lists other references that provide published clinical data regarding inhaled ciclesonide administered twice-daily. This list is not meant to be all-inclusive.

Reference	Treatment Arms*	Duration	Population
Weinbrenner A, Huneke D, Zschiesche M, et al. Circadian rhythm of serum cortisol after repeated inhalation of the new topical steroid ciclesonide. *J Clin Endocrinol Metab.* 2002;87:2160-2163.	-CIC 800 mcg QD_{AM} (ex-valve, 640 mcg ex-actuator) -CIC 800 mcg QD_{PM} (ex-valve, 640 mcg ex-actuator) -CIC 400 mcg BID (ex-valve, 320 mcg ex-actuator) -Placebo	Cross-over, each arm 7 days	N=12 21-28 years of age
Taylor DA, Jensen MW, Kanabar V, et al. A dose-dependent effect of the novel inhaled corticosteroid ciclesonide on airway responsiveness to adenosine-5'-monophosphate in asthmatic patients. *Am J Respir Crit Care Med.* 1999;160:237-243.	-CIC 50, 200, 800 mcg BID (dry powder formulation) -Placebo	Cross-over, each arm 14 days	N=37 18-45 years of age
Larsen BB, Nielsen LP, Engelstatter R, Steinijans V, Dahl R. Effect of ciclesonide on allergen challenge in subjects with bronchial asthma. *Allergy.* 2003;58:207-212.	-CIC 800 mcg BID (ex-valve, 640 mcg ex-actuator) -Placebo	Cross-over, each arm 1 week	N=15 19-46 years of age
O'Connor BJ, Sips P, Biberger C, Steinijans VW, Wurst W. Management of moderate to severe bronchial asthma by ciclesonide: a 12-week study [abstract 1120]. *Allergy.* 2002;57:S73.	-CIC 400 mcg BID (ex-valve, 320 mcg ex-actuator) -CIC 800 mcg BID (ex-valve, 640 mcg ex-actuator)	12 weeks	N=365 18-70 years of age
Erin EM, Zacharasiewicz AS, Nicholson GC, et al. Rapid anti-inflammatory effect of inhaled ciclesonide in asthma: a randomized, placebo-controlled study. *CHEST.* ePub April 10, 2008; DOI 10.1378/chest.07-2575.	-CIC 320 mcg QD_{AM} -CIC 640 mcg BID -Placebo	Cross-over, each arm 7 days	N=21 18-45 years of age

Reference	Treatment Arms*	Duration	Population
Bateman ED, Cheung D, Lapa e Silva J, Gohring UM, Schafer M, Engelstatter R. Randomized comparison of ciclesonide 160 and 640 µg/day in severe asthma. *Pulm Pharmacol Ther.* 2008;21:489-498.	-CIC 160 mcg QD_{AM} and placebo QD_{PM} -CIC 320 mcg BID	12 weeks	N=680 12-75 years of age

*Doses ex-actuator unless otherwise specified; CIC denotes ciclesonide.

Adults and Adolescents (12 and Older)-12 weeks Duration

Once-Daily Dosing Trials (Placebo-Control)

ALVESCO Inhalation Aerosol is an inhaled corticosteroid indicated for the maintenance treatment of asthma as prophylactic therapy to be administered twice a day in adult and adolescent patients 12 years of age and older. ALVESCO is NOT U.S. approved for once-daily use, the relief of acute bronchospasm, or for use in children under 12 years of age.

Please note when the U.S. FDA reviewed the twice-daily and once-daily dosing trials with ciclesonide, the FDA determined that once-daily dosing is NOT the optimum dosing regimen for ALVESCO. ALVESCO is FDA-approved for twice-daily administration up to 320 mcg (640 mcg/day). The use of ALVESCO with once-daily administration is considered off-label.

For complete Safety information, please refer to the enclosed Prescribing Information.

Efficacy and safety of ciclesonide metered-dose inhaler in adults and adolescents with mild to moderate persistent asthma administered once-daily. Data on File. Clinical Study Report 321; Marlborough, Mass: Sepracor Inc.

Objective:
To compare the safety and efficacy of ciclesonide 80 mcg, 160 mcg, and 320 mcg once daily in the morning to placebo in patients with mild-to-moderate persistent asthma.

Study Design and Population:
A Phase III, 12-week, multicenter, randomized, double-blinded, placebo-controlled, dose-response study was performed in patients with mild to moderate persistent asthma to determine the safety and efficacy of three dosing regimens of ciclesonide inhalation aerosol.[321] Patients were enrolled from 42 sites throughout the U.S. Patients were 12 years of age or older, had at least a 6 month history of asthma, and had an FEV_1 between 60% and 85% of predicted normal for patients previously controlled on a beta-agonist or between 65% and 100% for patients previously controlled on an inhaled corticosteroids after a 6-hour beta-agonist withholding period at the time of randomization. Patients were included in the trial if they had previously been stabilized on beta-agonist, leukotriene receptor antagonists, or inhaled corticosteroid therapy. Patients not receiving inhaled corticosteroids or those receiving any of the following low-to-moderate inhaled corticosteroid doses 30 days before screening were eligible to participate: 500 mcg/day or less fluticasone dry powder inhaler, 440 mcg/day or less fluticasone pressurized metered dose inhaler; 250 mcg/50 mcg or less fluticasone/salmeterol combination inhaler twice daily, or 1000 mcg/day or less budesonide, beclomethasone , flunisolide, or triamcinolone. Patients were required to be nonsmokers for at least 1 year (<10 pack-year smoking history) and have a reversibility of FEV_1 by 12% or more after 2 inhalations of albuterol or a documented history of 12% or greater reversibility within 1 year of screening. Patients were randomized to receive

MDI ciclesonide (ex-actuator) 80 mcg QD_{AM} (n = 133), ciclesonide 160 mcg QD_{AM} (n = 128), ciclesonide 320 mcg QD_{AM} (n = 131), or placebo (n = 134).

The primary efficacy endpoint was the change in AM pre-dose FEV_1 from baseline to Week 12 compared to placebo. Other study endpoints included changes in AM PEF, albuterol use, total asthma symptom scores, and changes in AQLQ. Treatment-emergent adverse events were monitored throughout the trial. Cortisol data (serum cortisol measurements upon low-dose cosyntropin stimulation and 24-hour urine cortisol measurements) were also collected in a subset of patients.

Results:
The age range was 12 to 72 years of age with a mean age of 36.6 years. The mean baseline FEV_1 percent predicted at baseline was 70.9%.

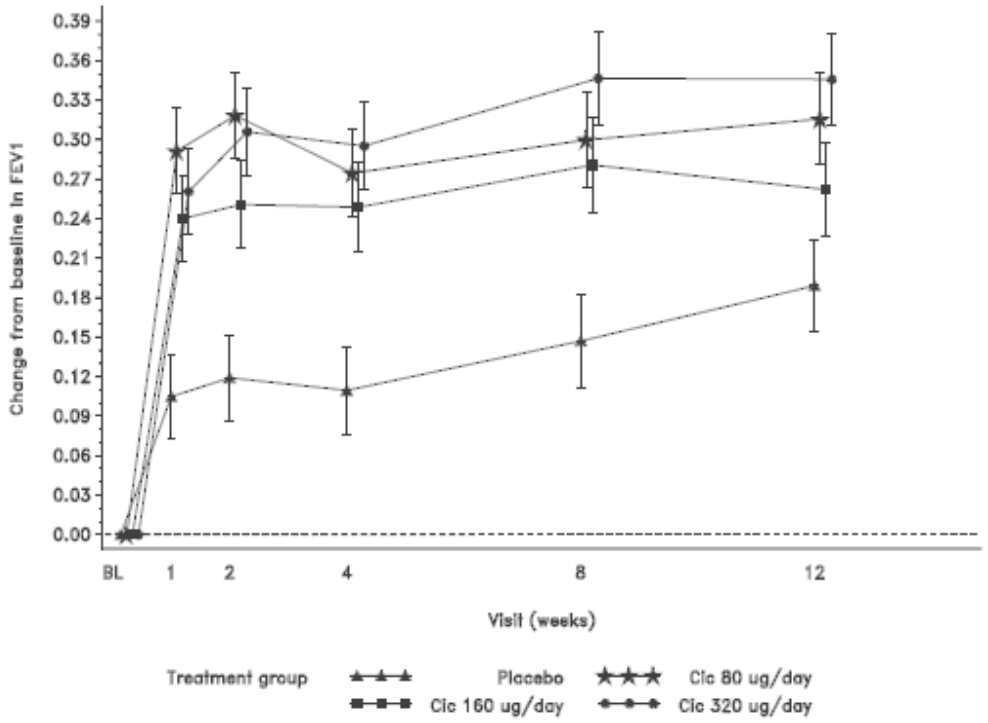
Both the ciclesonide 80 mcg QD_{AM} dose and the ciclesonide 320 mcg QD_{AM} dose had a statistically significant improvement in FEV_1 from baseline to Week 12 compared to placebo. Ciclesonide 160 mcg QD_{AM} did not significantly improve FEV_1 compared to placebo (see **Table 2.2.6 and Figure 2.2.4**). Morning peak expiratory flow rate improved significantly in all treatment groups compared to placebo. Total asthma symptom scores and daily albuterol use decreased significantly in all treatment groups (see **Table 2.2.6**).

Table 2.2.6 below provides an overview of treatment differences compared to placebo in the primary and key secondary endpoints from baseline to Week 12.

Table 2.2.6: Summary of Treatment Differences of Ciclesonide MDI Versus Placebo MDI-ITT Population from Baseline to Week 12

	Treatment difference at Week 12 versus placebo LS mean (95% CI) p Value		
	CIC 80 mcg QD_{AM}	**CIC 160 mcg QD_{AM}**	**CIC 320 mcg QD_{AM}**
Primary efficacy variable FEV_1 (L)	0.12 (0.03, 0.21) 0.0123	0.07 (-0.03, 0.16) 0.1645	0.15 (0.06, 0.25) 0.0014
Key secondary efficacy variables AM PEF (L/min)	15.58 (5.25,25.90) 0.0032	18.93 (8.48,29.39) 0.0004	24.53 (14.16,34.90) 0.0001
Albuterol use (puffs/day)	-1.52 (-2.06,-0.97) 0.0001	-1.60 (-2.15,-1.04) 0.0001	-1.88 (-2.42,-1.33) 0.0001
Total asthma symptom score (0-8 scale)	-0.38 (-0.69, -0.08) 0.0146	-0.55 (-0.86, -0.24) 0.0006	-0.68 (-0.98, -0.37) 0.0001

Figure 2.2.4: Change in FEV_1 (L) from Baseline over 12 Weeks



Overall score and two of the four measures in the AQLQ (symptoms and emotional function) were statistically significantly improved in all three ciclesonide treatment groups compared to placebo. More than 40% of the patients in the CIC 80 mcg QD_{AM} and CIC 160 mcg QD_{AM} treatment groups and more than 50% of the patients in the CIC 320 mcg QD_{AM} achieved the MID for improvement, an increase of at least 0.05 in the overall score, compared to 30% in the placebo group.

Fewer patients permanently discontinued their treatment in the ciclesonide treatment groups (CIC 80 mcg- 3.8%, CIC 160 mcg- 7.0%, and CIC 320 mcg- 3.8%) compared to the placebo group (16.4%).

The frequency of treatment-emergent adverse events for all treatment groups was similar to placebo (53.7% in placebo group, 57.1% in the CIC 80 mcg group, 50.8% in the CIC 160 mcg group, and 50.4% in the CIC 320 mcg group). The most common (>7% of patients in any treatment group) treatment-emergent adverse events reported in the CIC 80 mcg, CIC 160 mcg, CIC 320 mcg and placebo groups were asthma aggravated (4.5%, 5.5%, 2.3% and 15.7%), nasopharyngitis (8.3%, 7.8%, 6.1% and 4.5%), and upper respiratory infection (8.3%, 6.3%, 5.3% and 7.5%).

The incidence of oropharyngeal adverse events was similar between groups (for CIC 80 mcg, CIC 160 mcg, CIC 320 mcg, and placebo groups: oral candidiasis 1.5%, 0%, 1.5% and 0%; pharyngitis 3.8%, 4.7%, 3.8%, and 4.5%; and hoarseness 0.8%, 0%, 0.8%, and 0.7%).

There were no significant differences from baseline to Week 12 in peak cortisol concentrations or 24-hour urinary cortisol concentrations for ciclesonide or placebo patients.

Conclusions:
Refer to the results section.

Efficacy and safety of ciclesonide metered-dose inhaler in adults and adolescents with mild to moderate persistent asthma administered once-daily. Data on File. Clinical Study Report 322; Marlborough, Mass: Sepracor Inc.

Objective:
To compare the safety and efficacy of ciclesonide 80 mcg, 160 mcg, and 320 mcg once daily in the morning to placebo in patients with mild-to-moderate persistent asthma.

Study Design and Population:
A Phase III, 12-week, multicenter, randomized, double-blinded, placebo-controlled, dose-response study was performed in patients with mild to moderate persistent asthma to determine the safety and efficacy of three dosing regimens of ciclesonide inhalation aerosol. Patients were enrolled from 40 sites throughout the U.S. Patients were 12 years of age or older, had at least a 6 month history of asthma, and had an FEV_1 between 60% and 85% of predicted normal for patients previously controlled on a beta-agonist or between 65% and 100% for patients previously controlled on an inhaled corticosteroids after a 6-hour beta-agonist withholding period at the time of randomization. Patients were included in the trial if they had previously been stabilized on beta-agonist, leukotriene receptor antagonists, or inhaled corticosteroid therapy. Patients not receiving inhaled corticosteroids or those receiving any of the following low-to-moderate inhaled corticosteroid doses 30 days before screening were eligible to participate: 500 mcg/day or less fluticasone dry powder inhaler, 440 mcg/day or less fluticasone pressurized metered dose inhaler; 250 mcg/50 mcg or less fluticasone/salmeterol combination inhaler twice daily, or 1000 mcg/day or less budesonide, beclomethasone, flunisolide, or triamcinolone. Patients were required to be nonsmokers for at least 1 year (<10 pack-year smoking history) and have a reversibility of FEV_1 by 12% or more after 2 inhalations of albuterol or a documented history of 12% or greater reversibility within 1 year of screening. Patients were randomized to receive MDI ciclesonide (ex-actuator) 80 mcg QD_{AM} (n = 124), ciclesonide 160 mcg QD_{AM} (n = 123), ciclesonide 320 mcg QD_{AM} (n = 124), or placebo (n = 118).

The primary efficacy endpoint was the change in AM pre-dose FEV_1 from baseline to Week 12 compared to placebo. Other study endpoints included changes in AM PEF, albuterol use, total asthma symptom scores, and changes in AQLQ. Treatment-emergent adverse events were monitored throughout the trial. Cortisol data (serum cortisol measurements upon low-dose cosyntropin stimulation and 24-hour urine cortisol measurements) were also collected in a subset of patients.

Results:
The age range was 11 to 79 years of age with a mean age of 36.5 years. The mean baseline FEV_1 percent predicted at baseline was 71.1%.

Ciclesonide 80 mcg QD_{AM}, 160 mcg QD_{AM}, and 320 mcg QD_{AM} had a statistically significant improvement in FEV_1 from baseline to Week 12 compared to placebo (see **Table 2.2.7 and Figure 2.2.5**). Morning peak expiratory flow rate improved significantly in the CIC 160 mcg and 320 mcg groups only compared to placebo. The reduction in daily albuterol use was significant in all CIC groups compared to placebo.

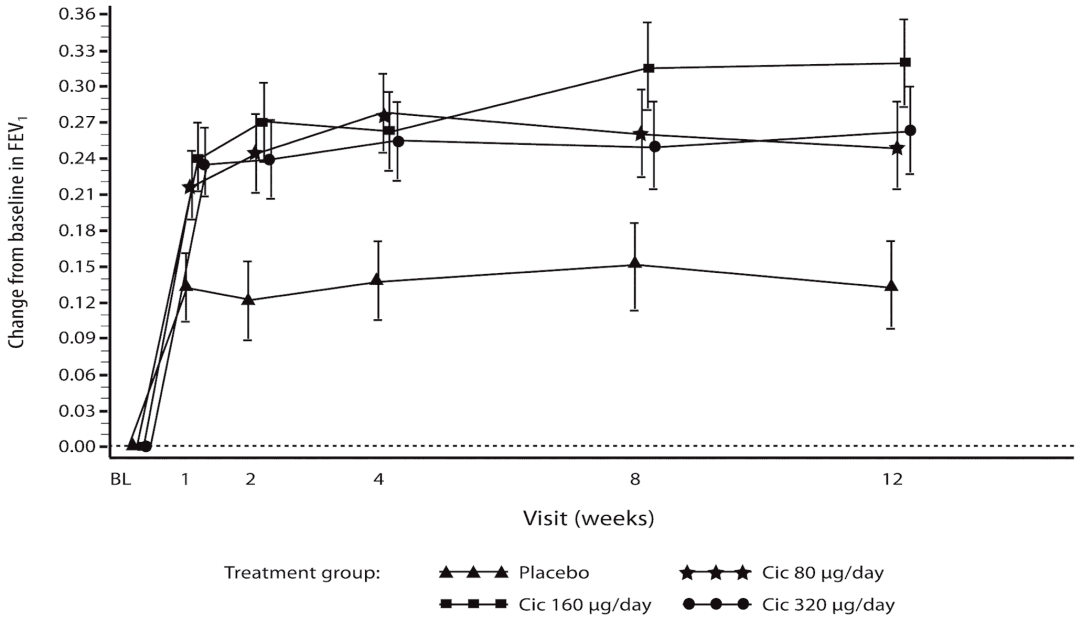
The total asthma symptom scores decreased significantly compared to placebo in the CIC 80 mcg and CIC 160 mcg treatment groups only (see **Table 2.2.7**).

Table 2.2.7 below provides an overview of treatment differences compared to placebo in the primary and key secondary endpoints from baseline to Week 12.

Table 2.2.7: Summary of Teatment Differences of Ciclesonide MDI Versus Placebo MDI-ITT Population from Baseline to Week 12

	Treatment difference at Week 12 versus placebo LS mean (95% CI) p Value		
	CIC 80 mcg QD_{AM}	**CIC 160 mcg QD_{AM}**	**CIC 320 mcg QD_{AM}**
Primary efficacy variable FEV_1 (L)	0.12 (0.02, 0.22) 0.0224	0.19 (0.09, 0.29) 0.0003	0.12 (0.02, 0.22) 0.0173
Key secondary efficacy variables AM PEF (L/min)	9.27 (-1.35, 19.89) 0.0871	26.8 (16.16, 37.52) 0.0001	12.89 (2.31, 23.47) 0.0171
Albuterol use (puffs/day)	-1.03 (-1.57, -0.49) 0.0002	-1.24 (-1.78, -0.70) 0.0001	-1.01 (-1.55, -0.48) 0.0002
Total asthma symptom score (0-8 scale)	-0.46 (-0.79, -0.13) 0.0060	-0.52 (-0.85, -0.19) 0.0020	-0.25 (-0.58, 0.08) 0.1346

Figure 2.2.5: Change in FEV_1 (L) from Baseline over 12 Weeks



Overall score and three of the four measures (symptoms, activity limitation, and emotional function) in the AQLQ were statistically significantly improved in the three ciclesonide treatment groups compared to placebo. More than 48% of the patients in the CIC 80 mcg QD_{AM}, CIC 160 mcg QD_{AM}, and CIC 320 mcg QD_{AM} treatment groups achieved the MID for improvement, an increase of at least 0.05 in the overall score, compared to 32% in the placebo group.

Fewer patients permanently discontinued their treatment in the ciclesonide treatment groups (CIC 80 mcg- 4.8%, CIC 160 mcg- 3.3%, and CIC 320 mcg- 4.0%) compared to the placebo group (14.4%).

Overall, the frequency of treatment-emergent adverse events was comparable for all treatment groups (CIC 80 mcg QD_{AM}, 62.1%; CIC 160 mcg QD_{AM}, 65.9%; CIC 320 mcg QD_{AM}, 65.3%; and placebo, 66.9%). The most common treatment-emergent adverse events (reported by >10% of patients in any treatment group) were nasopharyngitis (CIC 80 mcg QD_{AM}, 9.7%; CIC 160 mcg QD_{AM}, 10.6%; CIC 320 mcg QD_{AM}, 12.9%; and placebo, 10.2%), headache (CIC 80 mcg QD_{AM}, 8.1%; CIC 160 mcg QD_{AM}, 13.0%; CIC 320 mcg QD_{AM}, 12.9%; and placebo, 11.9%), upper respiratory infection (CIC 80 mcg QD_{AM}, 15.3%; CIC 160 mcg QD_{AM}, 7.3%; CIC 320 mcg QD_{AM}, 7.3%; and placebo, 12.7%), and asthma aggravated (CIC 80 mcg QD_{AM}, 8.1%; CIC 160 mcg QD_{AM}, 2.4%; CIC 320 mcg QD_{AM}, 2.4%; and placebo, 17.8%). The incidence of oropharyngeal adverse events was similar between groups (for CIC 80 mcg, CIC 160 mcg, CIC 320 mcg, and placebo groups: oral candidiasis 0.8%, 0%, 1.6% and 0.8%; pharyngitis 7.3%, 3.3%, 6.5%, and 5.9%; and hoarseness 0%, 0%, 0.8%, and 0%).

There were no significant differences from baseline to Week 12 in low-dose peak serum cortisol concentrations and 24-hour urinary free cortisol concentrations corrected for creatinine for ciclesonide patients compared to placebo patients.

Conclusions:
Refer to the results section.

Other Ciclesonide Once-daily Trials in Adults and Adolescents (non-Comparator Trials):
The following table lists other references that provide published clinical data regarding inhaled ciclesonide administered once-daily. This list is not meant to be all-inclusive.

Reference	Treatment Arms*	Duration	Population
Adachi M, Ishihara K, Inoue H, et al. Efficacy and safety of once-daily inhaled ciclesonide in adults with mild to moderate asthma: A double-blind, placebo-controlled study. *Respirology.* 2007;12:566-572.	-CIC 100, 200, 400 mcg QD_{PM} (ex-valve, 80 mcg, 160 mcg, 320 mcg ex-actuator) -Placebo	8 weeks	N=311 16-75 years of age
Langdon CG, Adler M, Mehra S, Alexander M, Drollmann A. Once-daily ciclesonide 80 or 320 µg for 12 weeks is safe and effective in patients with persistent asthma. *Respir Med.* 2005;99:1275-1285.	-CIC 80, 320 mcg QD_{AM} -Placebo	12 weeks	N=360 18-70 years of age
Chapman KR, Patel P, D'Urzo AD, et al. Maintenance of asthma control by once-daily inhaled ciclesonide in adults with persistent asthma. *Allergy.* 2005;60:330-337.	-CIC 160, 640 mcg QD_{AM} -Placebo	12 weeks	N=329 18-70 years of age
Postma DS, Sevette C, Martinat Y, Schlosser N, Aumann J, Kafe H. Treatment of asthma by the inhaled corticosteroid ciclesonide given either in the morning or evening. *Eur Respir J.* 2001;17:1083-1088.	-CIC 200 mcg QD_{AM} (ex-valve, 160 mcg ex-actuator) and $Placebo_{PM}$ -CIC 200 mcg QD_{PM} (ex-valve, 160 mcg ex-actuator) and $Placebo_{AM}$	8 weeks	N=209 18-75 years of age
Subbarao P, Duong M, Adelroth E, et al. Effect of ciclesonide dose and duration of therapy on exercise-induced bronchoconstriction in patients with asthma. *J Allergy Clin Immunol.* 2006;117:1008-1013.	-CIC 40 and 160 mcg QD_{PM} -CIC 80 and 320 mcg QD_{PM}	Cross-over, each arm 3 weeks	N=26 12-30 years of age
Gauvreau GM, Boulet LP, Postma DS, et al. Effect of low-dose ciclesonide on allergen-induced responses in subjects with mild allergic asthma. *J Allergy Clin Immunol.* 2005;116:285-291.	-CIC 40, 80 mcg QD_{AM} -Placebo	Cross-over, each arm 7 days	N=22 19-58 years of age

Reference	Treatment Arms*	Duration	Population
Cohen J, Douma WR, ten Hacken NHT, Vonk JM, Oudkerk M, Postma DS. Ciclesonide improves measures of small airway involvement in asthma. *Eur Respir J.* 2008;31(6):1213-1220.	-CIC 320 mcg QD_{AM} -Placebo	5-6 weeks	N=16 18-60 years of age
Wilson AM, Duong M, Pratt B, Dolovich M, O'Byrne PM. Anti-inflammatory effects of once daily low dose inhaled ciclesonide in mild to moderate asthmatic patients. *Allergy.* 2006;61:537-542.	-CIC 160 mcg QD_{AM} -Placebo	Cross-over, each arm 4 weeks	N=20 18-71 years of age

*Doses ex-actuator unless otherwise specified; CIC denotes ciclesonide

Ciclesonide Twice-Daily Comparator Trials

ALVESCO Inhalation Aerosol is an inhaled corticosteroid indicated for the maintenance treatment of asthma as prophylactic therapy to be administered twice a day in adult and adolescent patients 12 years of age and older. ALVESCO is NOT U.S. approved for once-daily use, the relief of acute bronchospasm, or for use in children under 12 years of age.

ALVESCO is FDA-approved for twice-daily administration up to 320 mcg (640 mcg/day).

For complete Safety information, please refer to the enclosed Prescribing Information.

Comparison to Fluticasone propionate- Efficacy and Safety

Bateman E, Linnhof AE, Homik L, Freudensprung U, Smau L, Engelstatter R. Comparison of twice-daily inhaled ciclesonide and fluticasone propionate in patients with moderate-to-severe persistent asthma. *Pulm Pharmacol Ther*. 2008;21:264-275. Clinical Study Report 103/2005.

Objective:
Investigate the efficacy of comparable doses of ciclesonide and fluticasone in maintaining asthma control in patients with moderate-to-severe asthma.

Study Design and Population:
An open-label, randomized, parallel-group study was performed in patients with moderate-to-severe persistent asthma (ATS-defined). A total of 100 centers in Europe, Canada, and South Africa participated in this trial. Patients 12 years of age and older with at least a 6-month history of asthma were enrolled if they had been stabilized on inhaled corticosteroids for at least four weeks prior to randomization and had an FEV_1 of at least 80% predicted normal value. The dose of corticosteroids in the period prior to randomization was 500-1000 mcg/day (stable dose for at least 4 weeks) of fluticasone propionate or equivalent. Patients continued their corticosteroid treatment until randomization at which point they discontinued their previous corticosteroid and were randomized to receive HFA MDI formulations of either inhaled ciclesonide 320 mcg (ex-actuator) BID (n = 255) or fluticasone propionate 330 mcg (ex-actuator) BID (n = 273) for 6 months. The primary efficacy parameter was change in AM pre-dose FEV_1 from baseline to Week 24 and the drop-out rate due to asthma exacerbation was analyzed as a co-primary variable. Efficacy measures also included change in FVC, FEV_1 percent predicted, PEF, asthma symptom scores, rescue medication (salbutamol) use, and AQLQ scores. Treatment-emergent adverse events, including oropharyngeal events (as key secondary variables), were monitored throughout the trial.

Results
Patients were between the ages of 12 and 75 years with a median age range of 43 to 44 years. The mean FEV_1 percent predicted at baseline was 93.0%.

The increase in AM pre-dose FEV_1 from baseline to Week 24 for CIC was 0.011 L and for FP was 0.024 L. The AM pre-dose FEV_1 change from baseline treatment difference (LS mean) between the CIC and FP treatment groups was non-significant [-0.013 L (-0.070, 0.044), $p>0.05$] indicating non-inferiority. Asthma exacerbations that required treatment with an oral corticosteroid occurred in 6 ciclesonide patients and 7 fluticasone patients. The LS mean change in FVC from baseline to Week 24 between the CIC and FP treatment groups also demonstrated non-inferiority (-0.001 L for CIC and 0.044 L for FP, $p>0.05$). Morning, evening and site-measured peak expiratory flow rate improved in both of the treatment groups significantly (change from baseline 8.6 L/min for CIC and 8.4 L/min for FP, both $p<0.05$). A reduction from baseline in asthma symptom scores (-0.14 for both CIC and FP, $p<0.0001$ for CIC and $p=0.0001$ for FP) and rescue medication use (-0.07 puffs/day for CIC, $p=0.0005$ and -0.14 puffs/day for FP, $p<0.0001$) was seen in both treatment groups. The overall AQLQ score improved significantly from baseline in both treatment groups (0.18 for CIC and 0.15 for FP, both $p<0.05$).

The frequency of treatment-emergent adverse events was similar between groups (61.2% for CIC and 63.0 for FP). The most common adverse events that occurred in ≥4% in either treatment group were nasopharyngitis (11.8% for CIC and 8.8% for FP), upper respiratory tract infection (8.2% for CIC and 7.3% for FP), pharyngolaryngeal pain (4.3% and 4.4%), asthma (3.9% for CIC and 5.5% for FP), bronchitis (3.5% for CIC and 4.0% for FP), influenza (3.1% for CIC and 4.4% for FP), headache (2.4% for CIC and 4.4% from FP), dysphonia (see below), and oral candidiasis (see below).

Overall, oropharyngeal adverse events were significantly less in the ciclesonide group compared to the fluticasone group (dysphonia: 3.1% vs. 9.2% and oral candidiasis: 2.0% vs. 4.8%; $p=0.0023$).

Conclusions:
Refer to the results section.

Comparison to Fluticasone propionate- Safety

Szefler S, Rohatagi S, Williams J, Lloyd M, Kundu S, Banerji D. Ciclesonide, a novel inhaled steroid, does not affect hypothalamic-pituitary-adrenal axis function in patients with moderate-to-severe persistent asthma. *CHEST.* 2005;128:1104-1114. Clinical Study Report 103.

Objective:
Investigate the effect of ciclesonide twice-daily on HPA-axis in patients with moderate-to-severe asthma.

Study Design and Population:
A single-center (U.S), randomized, double-blind, placebo-controlled, double-dummy, multiple-dose, parallel-group safety study was performed in adults 18 years of age and older (n = 59) with moderate to severe asthma (ATS defined; FEV_1 between 40% and 80% of predicted). Patients also had to have normal HPA-axis function, defined as a basal AM serum cortisol level of at least 5 mcg/dL and a serum cortisol level of at least 18 mcg/dL upon low-dose (1 mcg) cosyntropin stimulation. Groups of 12 patients were randomized to receive inhaled ciclesonide HFA MDI 320 mcg BID, ciclesonide HFA MDI 640 mcg BID, fluticasone propionate CFC MDI 440 mcg BID, fluticasone propionate CFC MDI 880 mcg BID (all ex-actuator doses), or placebo for 29 days. The primary outcome measurement was the change from baseline to Day 29 in serum cortisol concentration $AUC_{0\text{-}24hr}$. Secondary outcomes included serum cortisol concentration after low-dose cosyntropin stimulation and 24-hour urinary cortisol concentration. Treatment-emergent adverse events were monitored throughout the trial.

Results: Safety
Patients were between 22 and 66 years of age with a mean age of 43 years. The baseline FEV_1 percent predicted was 56-65%. The mean baseline serum AUC levels ranged from 192.0 to 246.4 mcg*hr/dL.

Following 29 days of treatment, the primary endpoint, mean change from baseline in 24-hour serum cortisol AUC in mcg*hr/dL was 18.5, -4.1, and 0.7 for CIC 320 mcg BID, CIC 640 mcg BID, and FP 440 mcg BID compared to -19.6 for placebo. This change was not significant for all groups except the high dose fluticasone propionate group (-58.6 mcg*hr/dL) where there was a statistically significant suppression of serum cortisol $AUC_{0\text{-}24hr}$ from baseline compared to the ciclesonide 640 mcg BID group (p=0.0013) and placebo group (p=0.0009). The effects observed with the comparator corticosteroid validate the sensitivity of the study to assess the effect of ciclesonide on the HPA axis. There were no significant differences among treatment groups in response to cosyntropin stimulation. There was a significant increase in 24-hour urinary cortisol concentration in the ciclesonide 320 mcg BID group compared to placebo (p=0.0224). There were no statistically significant differences in 24-hour urinary cortisol concentration for the other treatment groups when compared to placebo.

The incidence of treatment-emergent adverse events was similar for all treatment groups compared to placebo (58.3% for both ciclesonide treatment groups, 41.7% for FP 440 mcg BID, 58.3% for FP 880 mcg BID, and 58.3% for the placebo group). The most common adverse treatment-emergent events that occurred were headache (6 placebo patients, 10 CIC patients and 9 FP patients), sinus headache (0 placebo patients, 1 CIC patient and 2 FP patients), influenza-like illness (2 placebo patients, none from other groups), and sinusitis (3 FP patients, none from other groups).

Conclusions:
Refer to the results section.

Other Trials in Adults and Adolescents Comparing Twice-daily Ciclesonide to Fluticasone:

The following table lists other references that provide published clinical data regarding inhaled ciclesonide administered twice-daily compared to fluticasone propionate. This list is not meant to be all-inclusive.

Reference	Treatment Arms*	Duration	Population
Derom E, Van De Velde V, Marissens S, Engelstatter R, Vincken W, Pauwels R. Effects of inhaled ciclesonide and fluticasone propionate on cortisol secretion and airway responsiveness to adenosine 5'monophosphate in asthmatic patients. *Pulm Pharmacol Ther.* 2005;18:328-336.	-CIC 320, 640 mcg QD_{PM} -CIC 640 mcg BID -FP440, 880 mcg BID -Placebo	Cross-over, each arm 9 days	N=26 18-60 years of age
Tamm M, Dusser D, Fernandez J, Hellwig M, Engelstatter R. Efficacy and tolerability of ciclesonide compared with fluticasone propionate in patients with well-controlled moderate to severe persistent asthma [abstract]. *Allergy.* 2007;62(Suppl. 83):144.	-CIC 320 mcg BID -FP 500 mcg BID (ex-valve)	24 weeks	N=503 18-75 years of age
FitzGerald JM, Magnussen H, Engelstatter R. Comparative safety and efficacy of ciclesonide and fluticasone propionate in the management of adult persistent asthma [poster]. Presented at CHEST 2007, Oct. 20-25, 2007; Chicago, IL.	-CIC 320 mcg QD -CIC 320, 640 mcg BID -FP 220, 440, 880 mcg BID	3 weeks	N=100 18-70 years of age
Lipworth BJ, Kaliner MA, LaForce CF, et al. Effect of ciclesonide and fluticasone on hypothalamic-pituitary-adrenal axis function in adults with mild-to-moderate persistent asthma. *Ann Allergy Asthma Immunol.* 2005;94:465-472.	-CIC 320 mcg QD_{PM} -CIC 320 mcg BID -FP 440 mcg BID	12 weeks	N=164 18 and older
Lee DKC, Fardon TC, Bates CE, Haggart K, McFarlane LC, Lipworth, BJ. Airway and systemic effects of hydrofluoroalkane formulations of high-dose ciclesonide and fluticasone in moderate persistent asthma. *CHEST.* 2005;127:851-860.	-CIC 160 mcg BID -FP 220 mcg BID	4 weeks	N=21 Adults (mean age: 43 years)

* Doses ex-actuator unless otherwise specified
CIC denotes ciclesonide, FP- fluticasone propionate, SAL-salmeterol

Comparison to Beclomethasone dipropionate- Efficacy and Safety

Adachi M, Ishihara K, Inoue H, et al. Efficacy and safety of inhaled ciclesonide compared with chlorofluorocarbon beclomethasone diproprionate in adults with moderate to severe persistent asthma. *Respirology*. 2007;12:573-580. Clinical Study Report 184/2004.

Objective:
To evaluate the safety and efficacy of ciclesonide in hydrofluoroalkane (HFA) compared with beclomethasone in a chlorofluorocarbon (CFC) formulation in adult patients with moderate to severe asthma (defined by JGPMA).

Study Design and Population:
This was a multicenter (59 Japanese sites), randomized, open-label, parallel-group, comparative trial. Patients aged between 16 to 75 years with moderate to severe asthma according to the Japanese Guidelines on the Prevention and Management of Asthma who had been treated with ≥800 mcg/day of beclomethasone-CFC or ≥400 mcg/day of fluticasone propionate for more than four weeks were included in the study. Patients were required to have a mean morning PEF during the last week of the baseline period of[m1] ≤80% of the predicted PEF, and reversibility of airflow limitation of ≥15%. During a four-week baseline period, eligible patients received beclomethasone-CFC at a dose of 800 mcg/day. Following the baseline period, patients were randomized to treatment with ciclesonide-HFA 320 mcg (ex-actuator) without a spacer once daily in the evenings (n = 106), ciclesonide-HFA 320 mcg (ex-actuator) without a spacer twice daily (n = 107), or beclomethasone-CFC 400 mcg (ex-valve) with spacer twice daily (n = 106) for 8 weeks.

The primary efficacy endpoint was the change in morning PEF from baseline after 8 weeks. Secondary efficacy endpoints included changes in evening PEF, the use of rescue medication, and change in asthma score. FEV_1 and FVC were assessed at follow-up visits at week 4 and week 8. Patients recorded their morning and evening PEF, the use of rescue medication, and asthma symptom score in patient daily diaries.

Results:
The average mean patient age range was 51.6 to 52.4 years of age (range 36 to 68 years). The average FEV_1 percent predicted at baseline was between 67.3% and 70.5%.

Morning PEF increased from baseline by 16.02 L/min in the CIC QD_{PM} group, 23.98 L/min in the CIC BID group, and 5.91 L/min in the BDP group. Superiority was demonstrated in the CIC BID group compared to the BDP group ($p<0.001$). Non-inferiority was demonstrated in the CIC QD_{PM} group compared to the BDP group ($p<0.001$). The change in the morning PEF was greater in the CIC BID group than in the CIC QD_{PM} group, although the difference was not statistically significant ($p=0.112$). Evening PEF increased from baseline by 9.17 L/min in the CIC QD_{PM} group, 18.69 L/min in the CIC BID group, and 5.37 L/min in the BDP group. The increase from baseline in evening PEF for the CIC BID group was significantly greater than that for the BDP group ($p=0.021$). The use of rescue medication remained at the same level as

during the baseline period in the CIC QD_{PM} group (-0.01 puffs/day) and BDP group (+0.07 puffs/day), whereas it decreased in the CIC BID group (-0.44 puffs/day). The difference in the use of rescue medication was significant between the CIC BID group compared to the BDP group (p=0.007) and compared to the CIC QD_{PM} group (p=0.029). Asthma score decreased over time in both of the ciclesonide treatment groups compared to BDP. The differences in score between the CIC BID group and the BDP group were significant at week 8 (p=0.008).

The frequency of treatment-emergent adverse events that occurred in this trial were comparable between treatment groups (62.3% for CIC QD_{PM}, 67.3% for CIC BID, 56.6% for BDP). Adverse events occurring in 3% or more of patients in any group included nasopharyngitis (29.2% CIC QD, 37.4% CIC BID, 35.9% BDP), upper respiratory tract inflammation (8.5% CIC QD, 7.5% CIC BID, 6.6% BDP), headache (1.9% CIC QD, 5.6% CIC BID, 1.9% BDP), and pharyngitis (0.9% CIC QD, 3.7% CIC BID, 3.8% BDP). Oral candidiasis was not reported and mild hoarseness occurred rarely in patients (1 patient in CIC QD_{PM}, 3 patients in CIC BID, and 1 patient in BDP).

Conclusions:
Refer to the results section.

Comparison to Beclomethasone dipropionate- Safety

Safety of ciclesonide compared to beclomethasone over 12 months. Data on File. Clinical Study Report 3027; Marlborough, Mass: Sepracor Inc.

Objective:
Compare the effects of inhaled ciclesonide-HFA 320 mcg twice-daily and beclomethasone-HFA 320 mcg twice daily on lens opacification in adult subjects with moderate to severe persistent asthma over 12 months.

Study Design and Population:
A multicenter, multinational, active-controlled, double-blind, randomized (1:1) parallel-group non-inferiority trial was performed in adults patients 18 years and older with a history of moderate to severe persistent asthma for a duration of at least 2 months prior to screening. Patients were also required to have a forced expiratory volume in one second (FEV_1) of ≥40% and ≤85% of predicted at screening, documented use of inhaled corticosteroid therapy at any dose for at least one month prior to screening, and be a non-smoker for at least the past year and less than a 10-pack year history if a previous smoker. A total of 1568 patients were randomized to receive ciclesonide HFA (n=785) MDI 320 mcg twice daily (ex-actuator) OR beclomethasone HFA (n=783) MDI 320 mcg twice daily (ex-actuator).

The primary outcome measure was the occurrence of a Class I lens event for nuclear opalescence, cortical, or posterior subcapsular lens opacification within 12 months. Lens events were identified according to a protocol-specified change in lens opacification using the Lens Opacities Classification System III (LOCS III) for grading lens opacities, or the occurrence of cataract surgery. Secondary outcomes were: change from baseline at 12 months in LOCS III grade for (a) nuclear opalescence, (b) cortical opacity, (c) posterior subcapsular opacity; occurrence of a Class II lens event or cataract surgery within 12 months in either eye; occurrence of a Class III lens event or cataract surgery within 12 months in either eye; change from baseline at 12 months in best-corrected visual acuity (BCVA); change from baseline at 12 months in intraocular pressure (mm Hg). In addition to ophthalmologic measurements, pulmonary function (asthma control) and treatment-emergent adverse events were also assessed over the duration of the study.

The proportion of subjects with the primary endpoint of a Class I event in the treatment group was estimated by the life-table estimate of the event at Month 12, using the modified intent-to-treat (mITT) population. Non-inferiority was assessed by comparing the upper bound of the one-sided 97.5% confidence interval of the risk ratio with the non-inferiority bound (NIB). For purposes of consistency, analyses were also performed for the per-protocol population.

Results:
The mean subject age was 43.1 years. There were no relevant differences between the two groups in any of the demographic characteristics at screening. Additionally, baseline ophthalmologic characteristics were comparable between the two groups.

In the primary endpoint analysis, CIC was non-inferior to BDP according to life table estimates for the mITT population ($p<0.0001$). The estimated relative risk ratio of CIC to BDP for Class I lens events was 0.940 and the upper bound of the one-sided 97.5% confidence interval was 1.077, which was lower than the prespecified NIB of 1.333. Therefore, CIC met the criteria for non-inferiority versus BDP. Analyses for primary endpoint by life table estimates for the per-protocol population also confirmed non-inferiority of CIC to BDP.

For the secondary endpoints of Class II, sustained Class II, and Class III lens events were all lower than the respective prespecified NIBs. The relative risk ratios for each of these endpoints were all below 1. Mean maximum changes (least square means) from baseline in LOCS III grade during the study in either eye were comparable in the two treatment groups for each type of opacity: (a) nuclear opalescence- CIC 0.22, BDP 0.23; (b) cortical opacity- CIC 0.14, BDP 0.16; (c) posterior subcapsular CIC 0.06, BDP 0.05. For each type of opacity, the mean change from baseline at Month 12 in LOCS III grade was lower than the maximum changes from baseline in LOCS III grade over the course of the study. These changes were comparable between treatment groups. Changes from baseline in BCVA and median intraocular pressure were not clinically relevant and were comparable between the two groups.

The increase in FEV_1 between baseline and end of study was slightly lower in the CIC group than in the BDP group (1.14 % predicted vs. 1.76 % predicted, respectively) although there was no significant difference between the groups (95% CI: 1.497, 0.249).

The percentage of subjects with treatment-emergent adverse events was comparable in the CIC and BDP groups (83.5% and 85.6%, respectively). The most common adverse event in the CIC group was nasopharyngitis (20.9%, compared to 17.5% in the BDP group), and in the BDP group was upper respiratory tract infection (19.1%, compared to 19.5% in the CIC group). Other common adverse events included sinusitis, asthma, and headache, all of which had a frequency of >10% in both treatment groups. There was no sign of ocular toxicity associated with CIC compared to BDP.

Conclusions:
Refer to the results section.

Comparator Trials- Key Once-Daily Evaluations

ALVESCO Inhalation Aerosol is an inhaled corticosteroid indicated for the maintenance treatment of asthma as prophylactic therapy to be administered twice a day in adult and adolescent patients 12 years of age and older. ALVESCO is NOT U.S. approved for once-daily use, the relief of acute bronchospasm, or for use in children under 12 years of age.

Please note when the U.S. FDA reviewed the twice-daily and once-daily dosing trials with ciclesonide, the FDA determined that once-daily dosing is not the optimum dosing regimen for ALVESCO. ALVESCO is FDA-approved for twice-daily administration up to 320 mcg (640 mcg/day). The use of ALVESCO with once-daily administration is considered off-label.

For complete Safety information, please refer to the enclosed Prescribing Information.

Comparisons of Once-daily Ciclesonide to Fluticasone propionate

Magnussen H, Hofman J, Staneta P, Lawo J-P, Hellwig M, Engelstatter R. Similar efficacy of ciclesonide once daily versus fluticasone propionate twice daily in patients with persistent asthma. *J Asthma*. 2007;44:555-563. Clinical Study Report 369/2003.

Objective:
To compare the safety and efficacy of once-daily ciclesonide (80 and 160 mcg) in the evening with that of fluticasone (88 mcg) twice-daily in patients with persistent asthma.

Study Design and Population:
This 12-week, randomized, double-blind, double-dummy, three-arm, parallel group, non-inferiority study was conducted in patients 12 years of age and older diagnosed with persistent asthma (per ATS) for at least 6 months. Patients were recruited from 91 centers throughout Europe. To be eligible, patients previously treated with rescue medication only were required to have an FEV_1 between 61% and 90% of predicted. Patients previously treated with inhaled corticosteroids (maximum daily dose of 250 mcg fluticasone propionate or equivalent) were required to have an FEV_1 between 81% and 105% of predicted. For those patients previously treated with asthma medications other than inhaled corticosteroids (leukotriene antagonists and/or inhaled cromones), FEV_1 had to be between 61% and 105% of predicted. Patients were randomized to receive ciclesonide 80 mcg QD_{PM} (n = 278), ciclesonide 160 mcg QD_{PM} (n = 271) or MDI fluticasone propionate 88 mcg BID (n = 259) for 12 weeks.

The primary efficacy variables were the change in FEV_1 from baseline to the end of treatment and the change in nighttime asthma symptom score from baseline to the end of treatment. Secondary efficacy variables included morning PEF, rescue medication use, and days with asthma control (defined as asthma symptom-free and rescue medication-free days). Treatment-emergent adverse events were monitored throughout the trial.

Results:
The patient age range was 12 to 75 years with a mean patient age of 31 years. The mean FEV_1 percent predicted at baseline was 78-79%.

After the 12-week treatment period, the CIC 80, CIC 160, and FP groups achieved similar improvements in FEV_1 (0.412 L, 0.378 L, and 0.437 L, respectively; $p<0.0001$ for all). Both doses of ciclesonide were found to be non-inferior to fluticasone 88 mcg BID. Nighttime asthma symptom score significantly improved from baseline for all treatment groups, as did daytime asthma symptom score (nighttime score: -0.25 for all groups, $p<0.0001$; daytime score: -0.43 for CIC 80, -0.36 for CIC 160, and -0.43 for FP, $p<0.0001$ for all groups). The improvements in morning PEF were significant for all groups ($p<0.0001$) with non-inferiority concluded for the CIC 160 group compared to the FP group. Evening PEF improved for all treatment groups ($p<0.0001$) and non-inferiority was determined for both CIC groups compared to the FP group. All three treatment groups also significantly reduced rescue medication use versus baseline (-0.58 puffs/day for CIC 80 and -0.57 puffs/day for CIC 160 and FP, $p<0.0001$ versus baseline for all groups), with no statistically significant differences among treatment groups. The days with asthma control were similar among all treatment groups with no statistically significant differences.

Treatment-emergent adverse events were reported in 25.2%, 24.4%, and 27.4% of patients in the CIC 80 group, CIC 160 mcg group, and FP group, respectively. Nasopharyngitis (CIC 80 2.2%, CIC 160 3.0%, and FP 5.8%), asthma (CIC 80 2.5%, CIC 160 1.9%, and FP 3.1%), allergic rhinitis (CIC 80 2.2%, CIC 160 1.9%, and FP 2.3%), bronchitis (CIC 80 2.2%, CIC 160 0.4%, and FP 0.8%), pharyngitis (CIC 80 2.5%, CIC 160 1.9%, and FP 1.2%), seasonal allergy (CIC 80 1.8%, CIC 160 3.0%, and FP 1.9%), and allergic rhinitis (CIC 80 2.2%, CIC 160 1.9%, and FP 2.3%) were among the most frequently reported adverse events in ≥2% of patients in any one of the treatment groups. The incidence of oral candidiasis and oral fungal infection was low (<1%) and similar among groups.

Conclusions:
Refer to the results section.

Buhl R, Vinkler I, Magyar P, et al. Comparable efficacy of ciclesonide once daily versus fluticasone propionate twice daily in asthma. *Pulm Pharmacol Ther.* 2006;19:404-412. Clinical Study Report 196/2002.

Objective:
To compare the safety and efficacy of once daily ciclesonide 160 mcg administered in the evening compared to that of twice daily fluticasone propionate 88 mcg in patients with asthma.

Study Design and Population:
This Phase III, multicenter (57 centers, Europe and South Africa), randomized, double-blind, double-dummy, parallel group, non-inferiority study was conducted in adolescents and adults patients with asthma. Eligible patients were 12 years of age and older with a diagnosis of asthma according to American Thoracic Society (ATS) guidelines for at least 6 months. Patients who were maintained on a constant dose of inhaled corticosteroids of up to 500 mcg/day beclomethasone or equivalent in the 4 weeks prior to the baseline period and who had a FEV_1 of 80 to 100% predicted were allowed to enter the baseline period. Patients were eligible for randomization if they had an FEV_1 between 50% and 90% of predicted after a 4-hour beta-agonist withholding period and decrease of 10% or more after inhaled corticosteroid withdrawal. Patients were randomized to receive HFA MDI formulations of either ciclesonide 160 mcg (ex-actuator) once daily in the evening (n = 266) or fluticasone propionate 88 mcg (ex-actuator) twice daily (n = 263) for 12 weeks.

The change in PM pre-dose FEV_1 from baseline to week 12 was the primary efficacy endpoint and the FVC and morning PEF were co-primary endpoints. Secondary efficacy endpoints included evening PEF, asthma symptom scores, and rescue medication use.

Results:
Patient age ranged between 12 and 74 years of age with a median age range of 38-39 years. The mean baseline FEV_1 percent predicted at baseline was 75%.

During the 12-week treatment period, CIC QD_{PM} and FP BID achieved similar improvements in FEV_1. Ciclesonide produced similar improvements from baseline in FEV_1 by the end of treatment (0.489 L and 0.499 L for CIC and FP patients, respectively, $p<0.0001$ for both groups). The LS mean difference in FEV_1 between CIC and FP treatments was -0.010 [95% CI (-0.085,0.066), p=0.801] demonstrating non-inferiority of CIC and FP. The change from baseline to end of treatment in FVC were similar in the CIC and FP groups (3.195 L and 3.322 L, respectively; $p<0.0001$ for both groups). The LS mean difference in FVC between CIC and FP treatments was 0.031 [95% CI (-0.053, 0.115), p=0.468]. The change from baseline in AM PEF was 33 L/min for CIC and 36 L/min for FP with an LS mean difference between treatments of -3 L/min [95% CI (-13, 7), p=0.582]. At 12 weeks, treatment with CIC and FP both produced significant decreases in the total asthma symptoms scores (-0.75 for CIC and -0.86 for FP, $p<0.0001$ for both groups). There were no significant differences in the change in asthma symptoms scores between treatment groups. The use of rescue medication from baseline decreased for both groups (-1.00

puffs/day for CIC and -1.21 puffs/day for FP, $p<0.0001$ for both) with no significant between-group differences.

Treatment-emergent adverse events were experienced by 36% of patients in the CIC group and 34% of patients in the FP group. The most frequently reported treatment-emergent adverse events in ≥4% of patients in both treatment groups were upper respiratory tract infection (8% in both groups), bronchitis (4% in CIC and 3% in FP), headache (3% in CIC and 4% in FP), and pharyngitis (4% in CIC and 3% in FP). Oral candidiasis or voice alteration occurred in 3 patients treated with fluticasone (1%) but in none of the patients receiving ciclesonide.

Conclusions:
Refer to the results section.

Other Once-daily Comparator Trials (Active-Control: Fluticasone propionate)

The following table lists other references that provide published clinical data regarding inhaled ciclesonide administered once-daily compared to fluticasone propionate. This list is not meant to be all-inclusive.

Reference	Treatment Arms*	Duration	Population
Richter K, Kanniess F, Biberger C, Nave R, Magnussen H. Comparison of the oropharyngeal deposition of inhaled ciclesonide and fluticasone propionate in patients with asthma. *J Clin Pharmacol.* 2005;45:146-152.	-CIC 800 mcg followed by FP 1000 mcg (ex-valve, CIC 640 mcg (ex-actuator) -FP 1000 mcg followed by CIC 800 mcg (ex-valve, CIC 640 mcg ex-actuator)	Cross-over 1 time dose, each arm	N=18 23-65 years of age
Pedersen S, O'Byrne P, Postma D. Comparative long-term efficacy of ciclesonide versus a fixed combination of fluticasone propionate and salmeterol in mild persistent asthma [abstract]. *Allergy.* 2007;62(Suppl. 83):11.	-CIC 160 mcg QD -FP/SAL 100/50 mcg BID (ex-valve) -Placebo	52 weeks	N=652 12-75 years of age
Boulet LP, Bateman ED, Voves R, Muller T, Wolf S, Engelstatter R. A randomized study comparing ciclesonide and fluticasone propionate in patients with moderate persistent asthma. *Respir Med.* 2007;101:1677-1686.	-CIC 320 mcg QD_{PM} -FP 200 mcg BID	12 weeks	N=474 12-75 years of age
Lee DKC, Haggart K, Currie GP, Bates CE, Lipworth BJ. Effects of hydrofluoroalkane formulations of ciclesonide 400 µg once daily vs fluticasone 250 µg twice daily on methacholine hyper-responsiveness in mild-to-moderate persistent asthma. *Br J Clin Pharmacol.* 2004;58(1):26-33.	-CIC 400 mcg QD_{AM} (ex-valve, 320 mcg ex-actuator) -FP 250 mcg BID (ex-valve)	4 weeks	N=23 Adults

Reference	Treatment Arms*	Duration	Population
Bladgen M, Rozen D, Vereecken G, Gruss C, Lawo J, Engelstatter R. Comparison of ciclesonide 160 µg once daily with fluticasone propionate 250 µg twice daily in maintenance therapy of patients with stable asthma [abstract]. *Allergy.* 2007;62(Suppl. 83):144.	-CIC 160 mcg QD -FP 250 mcg BID (ex-valve)	12 weeks	N=111 17-75 years of age
Zietkowski Z, Bodzenta-Lukaszyk A, Tomasiak MM, Szymanski W, Skiepko R. Effect of ciclesonide and fluticasone on exhaled nitric oxide in patients with mild allergic asthma. *Respir Med.* 2006;100:1651-1656.	-CIC 80, 160 mcg QD_{PM} -FP 100 mcg BID (ex-valve)	12 weeks	N=35 28-58 years of age
Kosztyla-Hojna B, Rutkowski R, Popko M. Vocal function of larynx in bronchial asthma patients treated with fluticasone propionate (FP) or ciclesonide (CIC). *Int Rev Allergol Clin Immunol.* 2007;13(2-3):61-68.	-CIC 160 mcg once -FP 500 mcg once (ex-valve)	One time dose	N=60 20-52 years of age
Knox A, Langan J, Martinot J-B, Gruss C, Hafner D. Comparison of a step-down dose of once-daily ciclesonide with a continued dose of twice-daily fluticasone propionate in maintaining control of asthma. *Curr Med Res Opin*. 2007;23:2387-2394.	-CIC 160 mcg QD_{PM} -FP 250 mcg BID (ex-valve)	12 weeks	N=111 17 years of age and older

* Doses ex-actuator unless otherwise specified
CIC-ciclesonide, FP- fluticasone propionate, SAL-salmeterol

Comparisons of Once-daily Ciclesonide to Budesonide

Hansel TT, Benezet O, Kafé H, et al. A multinational, 12-week, randomized study comparing the efficacy and tolerability of ciclesonide and budesonide in patients with asthma. *Clin Ther*. 2006;28:906-920. Clinical Study Report 193/2000.

Objective:
To compare the safety and efficacy of ciclesonide once daily in the morning (80 or 320 mcg) to that of budesonide (200 mcg) twice daily in patients with asthma.

Study Design and Population:
This was a 12-week, multicenter (62 sites throughout Europe), randomized, trial evaluating the efficacy and safety of ciclesonide compared to budesonide. This study was double-blind with respect to the ciclesonide dose and open-label for budesonide. Patients aged 12 to 75 with primarily mild to moderate asthma for ≥6 months as defined by the ATS were eligible to participate. Patients previously on inhaled corticosteroids were required to have at least a 10% decrease in FEV_1 after discontinuation of their corticosteroid during the run-in period. Following a 1- to 4-week run-in period during which patients were only allowed to use a short-acting beta-agonist, patients were randomized to receive ciclesonide 80 mcg (n = 182, ex-actuator) or 320 mcg (n = 195, ex-actuator) in the morning or budesonide dry powder inhaler 200 mcg (n = 177, ex-valve) twice daily for 12 weeks.

The primary endpoint was the change from baseline in AM pre-dose FEV_1 at 12 weeks. Secondary endpoints included changes from baseline in morning PEF, asthma symptoms scores, and use of rescue medication which were all recorded in patient daily diaries. Treatment-emergent adverse events and 24-hour urinary cortisol measurements were monitored throughout the trial.

Results:
The median patient age range was 38-45 years of age with all patients between the ages of 12 and 74. The mean FEV_1 percent predicted at baseline was approximately 72%.

Significant increases from baseline in FEV_1 were observed in all three treatment groups at 12 weeks of treatment (0.267 L for CIC 80, 0.256 L for CIC 320, and 0.355 L for BUD, all $p<0.001$ for all groups). Differences between the three treatment groups were not statistically significant, indicating the non-inferiority of ciclesonide to budesonide. Morning PEF was improved significantly at Week 12 from baseline in all three treatment groups (12 L/min, $p=0.008$ for CIC 80, 17 L/min, $p<0.001$ for CIC 320, and 21 L/min, $p<0.001$ for BUD). Differences in AM PEF between the three treatment groups were not statistically significant, indicating the non-inferiority of ciclesonide to budesonide. Over the 12-week treatment period, significant improvements from baseline were found in median daily asthma symptom scores in all three treatment groups (-0.43 for CIC 80, -0.62 for CIC 320, and -0.57 for BUD, $p<0.001$ for all groups). There were significant decreases from baseline in the mean number of puffs/day of rescue medication in all treatment groups at week 12 (-0.68, -1.00, and -1.04 with CIC 80, CIC 320, and BUD respectively, all $p<0.001$).

The percentage of patients with treatment-emergent adverse events was similar across all three treatment groups (36.8% for CIC 80, 40.8% for CIC 320, and 33.9% for BUD). The most frequently reported adverse events in ≥4% of patients were upper respiratory tract infection (11.5% in CIC 80, 5.1% in CIC 320, and 7.9% in BUD), asthma (4.4% in CIC 80, 6.1% in CIC 320, and 4.0% in BUD), bronchitis (3.8% in CIC 80, 6.1% in CIC 320, and 4.0% in BUD) and rhinitis (2.7% in CIC 80, 3.6% in CIC 320, and 4.5% in BUD).

The mean 24-hour urinary cortisol excretion (nmol/mmol creatinine) at Week 12 was statistically similar to baseline in both ciclesonide treatment groups (-0.54 for CIC 80 and +0.16 for CIC 320), but was significantly reduced from baseline in the budesonide treatment group (-1.42, $p<0.05$).

Conclusions:
Refer to the results section.

Niphadkar P, Jagannath J, Joshi JM, et al. Comparison of the efficacy of ciclesonide 160 µg QD and budesonide 200 µg BID in adults with persistent asthma: A phase III, randomized, double-dummy, open-label study. *Clin Ther.* 2005;27:1752-1763. Clinical Study Report 88/2003.

Objective:
To compare the efficacy of ciclesonide 160 mcg once daily in the morning or the evening to that of budesonide 200 mcg twice daily in adults with stable asthma pretreated with inhaled corticosteroids.

Study Design and Population:
This was a phase III, randomized, multicenter, double-blind, 3-arm, parallel-group study comparing ciclesonide (given in a double-blind, double-dummy regimen) with open label budesonide. Patients were enrolled from 11 sites in India. Patients between the ages of 18 and 69 years with a diagnosis of persistent asthma for at least 6 months that was maintained on a constant dose of inhaled corticosteroids for 4 weeks before baseline were eligible to participate. Patients were required to have a FEV_1 of $\geq$70% predicted, stable asthma, and good overall health. Eligible patients were randomized to receive HFA MDI formulations of ciclesonide 160 mcg (ex-actuator) in the morning (n = 140), ciclesonide 160 mcg (ex-actuator) in the evening (n = 131), or budesonide 200 mcg (ex-valve) BID (n = 134) for 12 weeks. All patients received either two inhalations of medication or placebo in the morning and the evening.

The primary efficacy endpoint was the difference in AM pre-dose FEV_1 from baseline to Week 12. Secondary endpoints included changes in FVC, AM PEF, asthma symptoms, and use of rescue medication. Treatment-emergent adverse events were monitored throughout the trial.

Results:
The median patient age range was 29 to 32 years of age. The mean FEV_1 percent predicted at baseline was 93%.

No significant differences were found among the treatment groups with regard to the change in AM pre-dose FEV_1 from baseline to Week 12 [LS mean for CIC vs. BUD was -0.036 L (-0.118, 0.045), p=0.383 for CIC 160 QD_{AM} and 0.022 L (-0.061,0.105), p=0.598 for CIC 160 QD_{PM}]. FVC and AM PEF were maintained during the 12 week period in all three treatment groups. No significant differences were found among the three treatment groups for the secondary endpoints of FVC [LS mean vs. BUD was 0.005 L (-0.084, 0.094), p=0.905 for CIC 160 QD_{AM} and 0.002 L (-0.088, 0.092), p=0.968 for CIC 160 QD_{PM}] and AM PEF [LS mean vs. BUD was -4.4 L/min (-16.4, 7.5), p=0.464 for CIC 160 QD_{AM} and 9.3 L/min (-2.8, 21.5), p=0.131 for CIC 160 QD_{PM}]. All three treatment groups maintained asthma symptom scores during the 12-week treatment period, and no significant differences were found among the treatment groups. The use of rescue medication was maintained versus baseline, and no significant differences were found between the treatment groups (percentage of days free of rescue medication was 89% for CIC QD_{AM}, 91% for CIC QD_{PM}, and 93% for BUD).

The occurrence of treatment-emergent adverse events was comparable for all treatment groups (17% for CIC QD_{AM}, 24% for CIC QD_{PM}, and 21% for BUD). The most commonly reported adverse events in ≥2% of patients in any treatment group were asthma aggravated (9.3% in CIC QD_{AM}, 9.9% for CIC QD_{PM}, and 10.5% for BUD), upper respiratory tract infection NOS (2.1% for CIC QD_{AM}, 3.1% for CIC QD_{PM}, and 3.8% for BUD), and rhinitis NOS (1.4% for CIC QD_{AM}, 0.8% for CIC QD_{PM}, and 3.0% for BUD). No oropharyngeal adverse events were reported in any of the three treatment groups.

Conclusions:
Refer to the results section.

Vermeulen JH, Gyurkovits K, Rauer H, Engelstätter R. Randomized comparison of the efficacy and safety of ciclesonide and budesonide in adolescents with severe asthma. *Respir Med*. 2007;101:2182-2191. Clinical Study Report 59/2005.

Objective:
To evaluate the safety and efficacy of ciclesonide 320 mcg once-daily administered in the evening compared with budesonide 800 mcg once-daily in the evening in adolescents with severe asthma.

Study Design and Population:
This multicenter, randomized, double-blind, double-dummy, parallel-group, non-inferiority trial was conducted in adolescent patients ages 12 to 17 years with severe asthma (as defined by GINA) for ≥6 months prior to screening. Patients were enrolled from 31 sites throughout Europe and South Africa. Patients not well controlled after constant treatment with a fixed dose of budesonide 400 mcg/day (or equivalent) for ≥4 weeks prior to study entry with an FEV_1 percent predicted >50% to <80% were eligible to participate in a 2-week run-in period prior to randomization. For entry into the treatment period at randomization, patients had to have an FEV_1 >50% and <80% of predicted and a ≥15% reversibility of FEV_1 after inhalation of salbutamol. During the 2-week run-in period, patients were treated with budesonide 400 mcg once daily in the evening to standardize treatment. Patients who met the entry criteria for the treatment period were randomly assigned in a 2:1 ratio to once daily ciclesonide 320 mcg (ex-actuator) in the evening (n = 272) or once daily budesonide 800 mcg (ex-valve, dry-powder inhaler) administered in the evening (n = 131). Salbutamol was used as rescue medication throughout the study as needed.

The primary efficacy variable was the change in PM pre-dose FEV_1 from baseline to Week 12 or the last recorded measurement. Secondary efficacy variables included change in AM PEF, asthma symptom scores, rescue medication use, and quality of life questionnaire. Treatment-emergent adverse events were monitored throughout the trial.

Results:
The median patient age range was 14 years of age. The mean FEV_1 percent predicted at baseline was between 73.1% and 73.2%.

At week 12, significant increases in FEV_1 from baseline were observed in both the CIC (0.505 L, p<0.0001) and BUD (0.536 L, p<0.0001) treatment groups. There were no significant differences between treatment groups [-0.031 (-0.138, 0.076)]. Morning PEF increased from baseline to Week 12 by 8.0 L/min in the CIC group (p=0.0424) and 4.9 L/min in the BUD group (p=not significant [NS]). Median asthma symptom scores were significantly reduced (-0.07 for CIC [p<0.0005] and -0.14 for BUD [p<0.0001]) during the study in both treatment groups, and there were no statistically significant differences between treatment groups. The median use of rescue medication was reduced to zero puffs per day in the CIC and BUD groups at Week 12. CIC and BUD significantly improved the overall score in the quality-of-life assessment by a comparable amount [0.19 for CIC (p=0.0001) and 0.18 for BUD (p=0.0056)].

Treatment-emergent adverse events occurred in 26.5% of CIC patients and 18.3% of BUD patients. The most commonly reported adverse events in ≥2% of patients in any treatment group included pharyngitis (CIC 5.9%, BUD 3.8%), asthma aggravated (CIC 3.3%, BUD 1.5%), nasopharyngitis (CIC 2.6%, BUD 0.8%) and upper respiratory tract infection (CIC 2.2%, BUD 2.3%). There were no cases of confirmed candidiasis or events of hoarseness in this trial.

Median 24-hour urine cortisol levels significantly decreased from baseline to Week 12 in the BUD group (15.9-13.7 nmol cortisol/mmol creatinine, p=0.0086). The change in the CIC group was not significant (15.9-16.5 nmol cortisol/mmol creatinine, p=0.1125). The difference between treatment groups was significant (p=0.0012).

Conclusions:
Refer to the results section.

Other Once-daily Comparator Trials (Active-Control: Budesonide)

The following table lists other references that provide published clinical data regarding inhaled ciclesonide administered once-daily compared to budesonide. This list is not meant to be all-inclusive.

Reference	Treatment Arms*	Duration	Population
Nave R, Zech K, Bethke TD. Lower oropharyngeal deposition of inhaled ciclesonide via hydrofluoroalkane metered-dose inhaler compared with budesonide via chlorofluorocarbon metered-dose inhaler in healthy subjects. *Eur J Clin Pharmacol.* 2005;61:203-208.	-CIC 800 mcg followed by BUD 800 mcg (ex-valve, CIC 640 mcg ex-actuator) -BUD 800 mcg followed by CIC 800 mcg (ex-valve, CIC 640 mcg ex-actuator)	One time dose	N=18 18-65 years of age
Kanniess F, Richter K, Bohme S, Jorres RA, Magnussen H. Effect of inhaled ciclesonide on airway responsiveness to inhaled AMP, the composition of induced sputum and exhaled nitric oxide in patients with mild asthma. *Pulm Pharmacol Ther.* 2001;14:141-147.	-CIC 400 mcg QD_{AM} (ex-valve, 320 mcg ex-actuator) -BUD 400 mcg QD_{AM} (ex-valve)	Cross-over, each arm 2 weeks	N=15 21-48 years of age
Boulet LP, Drollmann A, Magyar P, et al. Comparative efficacy of once-daily ciclesonide and budesonide in the treatment of persistent asthma. *Respir Med.* 2006;100:785-794.	-CIC 320 mcg QD_{AM} -BUD 320 mcg QD_{AM}	12 weeks	N=359 12-75 years of age
Ukena D, Biberger C, Steinijans V, et al. Ciclesonide is more effective than budesonide in the treatment of persistent asthma. *Pulm Pharmacol Ther.* 2007;20:562-570.	-CIC 320 mcg QD_{PM} -BUD 400 mcg QD_{PM}	12 weeks	N=399 12-75 years of age

* Doses ex-actuator unless otherwise specified
CIC-ciclesonide, BUD- budesonide

Pediatric Trials- Children 4 to 11 Years of Age

ALVESCO Inhalation Aerosol is an inhaled corticosteroid indicated for the maintenance treatment of asthma as prophylactic therapy to be administered twice a day in adult and adolescent patients 12 years of age and older. ALVESCO is NOT U.S. approved for once-daily use, the relief of acute bronchospasm, or for use in children under 12 years of age.

Please note when the U.S. FDA reviewed the twice-daily and once-daily dosing trials with ciclesonide, the FDA determined that once-daily dosing is not the optimum dosing regimen for ALVESCO. ALVESCO is FDA-approved for twice-daily administration up to 320 mcg (640 mcg/day). The use of ALVESCO with once-daily administration is considered off-label.

For complete Safety information, please refer to the enclosed Prescribing Information.

The following pediatric QD dosing trials were completed in patients 4 to 11 years of age and relevant safety information is cited in the ALVESCO Inhalation Aerosol prescribing information.

Pediatric QD Dosing Trials (12-weeks in Duration)

Efficacy and safety of ciclesonide metered-dose inhaler in children with mild to moderate persistent asthma administered once-daily. Data on File. Clinical Study Report 341; Marlborough, Mass: Sepracor Inc.

Gelfand W, Georgitis JW, Noonan M, Ruff ME. Once-daily ciclesonide in children: efficacy and safety in asthma. *J Pediatr.* 2006;148:377-383. Pooled data for Study Reports 341 and 342.

Objective:
To compare the efficacy and safety of once-daily inhaled ciclesonide (40 mcg, 80 mcg and 160 mcg) administered in the morning with placebo in children with persistent asthma of all severities.

Study Design and Population:
A double-blind, placebo-controlled, parallel-group trial evaluated the efficacy and safety of ciclesonide in patients ages 4 to 11 years of age. Patients were enrolled from 67 sites (U.S. and Mexico) and were required to have at least a 6 month history of asthma, as defined by the NHLBI guidelines. Patients were to be maintained on inhaled corticosteroids and/or leukotriene receptor antagonists and/or cromones (Stratum 1) or bronchodilators only (Stratum 2) for the 30 days prior to screening. At randomization, all patients were required to have a FEV_1 predicted value ≥40% and ≤90% after ≥6 hours without the use of a beta-2 agonist. For Stratum 1 patients, this FEV_1 had to be at least a 10% reduction in FEV_1 from the recorded baseline at screening. In addition, for Stratum 2 patients, one or more of the following had to occur: asthma symptom score was 3 or more for at least 3 of the 7 days prior to randomization, PEF variability >20% for at least

3 of the 7 days prior to randomization, or albuterol use was at least 2 puffs/day for at least 3 of the 7 days prior to randomization. Eligible patients were randomized to receive ciclesonide 40 mcg (n = 126), ciclesonide 80 mcg (n = 135), ciclesonide 160 mcg (n = 122), all doses as ex-actuator dosage, or placebo (n = 131) all once-daily. All doses were administered without a spacer, as a single puff in the morning.

The primary efficacy variable was change in AM pre-dose FEV_1 percent predicted between baseline and week 12, last observation carried forward (LOCF). Secondary efficacy variables included changes in FEV_1 and AM PEF from baseline to Week 12, total asthma severity rating score, rescue medication use, and quality of life assessments. Treatment-emergent adverse events were monitored throughout the trial. Serum cortisol upon low-dose cosyntropin stimulation and 24-hour urinary cortisol concentrations were also measured from baseline to Week 12 in a subset of patients.

Results:
The mean patient age was 8.1 years of age. The mean FEV_1 percent predicted at baseline was 67.9%.

The change from baseline to Week 12 (LOCF) in AM pre-dose FEV_1 percent predicted was 12.61% for placebo, 13.76% for CIC 40 (p=NS vs. placebo), 16.54% for CIC 80 (p=0.0460 vs. placebo), and 15.95% for CIC 160 (p=NS vs. placebo). FEV_1 improved significantly from baseline to Week 12 in the CIC 80 group (mean increase 0.32 L, p=0.0259 vs. placebo) but not in the CIC 40 and CIC 160 groups. Increases in AM PEF were statistically significant from baseline to Week 12 (LOCF) in the CIC 80 (mean increase 25.30 L/min, p=0.0003 vs. placebo, placebo mean increase 8.96 L/min) and CIC 160 (mean increase 18.66 L/min, p=0.0343 vs. placebo) treatment groups. The CIC 80 and CIC 160 groups demonstrated significant baseline to Week 12 (LOCF) improvement in 24-hour asthma severity rating scores compared with the placebo group (mean decrease -1.25 and -1.12, respectively, $p<0.05$ for both vs. placebo, placebo decrease was -0.52). The decrease in the mean number of albuterol puffs per day from baseline to Week 12 (LOCF) in two ciclesonide groups was significantly greater than was seen in the placebo group (CIC 80 -0.94 puffs/day, p=0.0002 vs. placebo and CIC 160 -0.88 puffs/day, p=0.0011 vs. placebo; placebo decrease was -0.12 puffs/day). Only the CIC 80 group resulted in statistically significant improvements in the overall Quality of life (PAQLQ) score from baseline to Week 12 (mean increase 0.77, p=0.0353 vs. placebo).

The incidence of treatment-emergent adverse events was comparable in all four treatment groups (CIC 40: 64.3%, CIC 80: 61.5%, CIC 160: 71.4%, placebo: 67.7%). The most common treatment-emergent adverse events that occurred in more than 10% of any patient group were asthma aggravated (CIC 40: 14.3%, CIC 80: 15.6%, CIC 160: 16.0%, and placebo: 21.5%), nasopharyngitis (CIC 40: 8.7%, CIC 80: 12.6%, CIC 160: 10.9%, and placebo: 11.5%), sinusitis (CIC 40: 11.1%, CIC 80: 11.9%, CIC 160: 7.6%, and placebo: 7.7%), and headache (CIC 40: 10.3%, CIC 80: 13.3%, CIC 160: 12.6%, and placebo: 13.1%).

There were no reports of hoarseness or oral candidiasis in this trial. Pharyngitis was reported in 6.3% of CIC 40, 8.1% of CIC 80, 6.7% of CIC 160, and 6.9% of placebo patients.

New lenticular opacity was reported in two patients in the placebo group at study endpoint and in one patient in the CIC 160 group 72 days after the last dose. There were no reports of glaucoma in this trial.

Decreases from baseline in serum cortisol concentration upon cosyntropin stimulation were seen in all CIC treatment groups, however, the p values were not determined due to small sample size (cortisol measurements were only done in a subset of patients at certain study sites). There was no consistent pattern of changes in 24-hour urinary free cortisol concentrations seen in any of the CIC treatment groups; the p values were not determined due to small sample size.

Conclusions:
Refer to the results section.

Efficacy and safety of ciclesonide metered-dose inhaler in children with mild to moderate persistent asthma administered once-daily. Data on File. Clinical Study Report 342; Marlborough, Mass: Sepracor Inc.

Gelfand W, Georgitis JW, Noonan M, Ruff ME. Once-daily ciclesonide in children: efficacy and safety in asthma. *J Pediatr.* 2006;148:377-383. Pooled data for Study Reports 341 and 342.

Objective:
To compare the efficacy and safety of once-daily inhaled ciclesonide (40 mcg, 80 mcg and 160 mcg) administered in the morning with placebo in children with persistent asthma of all severities.

Study Design and Population:
A double-blind, placebo-controlled, parallel-group trial evaluated the efficacy and safety of ciclesonide in patients ages 4 to 11 years of age. Patients were enrolled from 64 sites (54 in the U.S. and 10 in Poland) and were required to have at least a 6 month history of asthma, as defined by the NHLBI guidelines. Patients were to be maintained on inhaled corticosteroids and/or leukotriene receptor antagonists and/or cromones (Stratum 1) or bronchodilators only (Stratum 2) for the 30 days prior to screening. At randomization, all patients were required to have a FEV_1 predicted value ≥40% and ≤90% after ≥6 hours without the use of a $beta_2$-agonist. For Stratum 1 patients, this FEV_1 had to be at least a 10% reduction in FEV_1 from the recorded baseline at screening. In addition, for Stratum 2 patients, one or more of the following had to occur: asthma symptom score was 3 or more for at least 3 of the 7 days prior to randomization, PEF variability >20% for at least 3 of the 7 days prior to randomization, or albuterol use was at least 2 puffs/day for at least 3 of the 7 days prior to randomization. Eligible patients were randomized to receive ciclesonide 40 mcg (n = 130), ciclesonide 80 mcg (n = 126), ciclesonide 160 mcg (n = 134), all doses as ex-actuator dosage, or placebo (n = 127) all once-daily. All doses were administered without a spacer, as a single puff in the morning.

The primary efficacy variable was change in AM pre-dose FEV_1 percent predicted between baseline and week 12. Secondary efficacy variables included changes in FEV_1 and AM PEF from baseline to Week 12, total asthma severity rating score, rescue medication use, and quality of life assessments. Treatment-emergent adverse events were monitored throughout the trial. Serum cortisol upon low-dose cosyntropin stimulation was also measured from baseline to Week 12 in a subset of patients.

Results:
The mean patient age was 8.3 years of age. The mean FEV_1 percent predicted at baseline was 68.8%.

The change from baseline to Week 12 (LOCF) in FEV_1 percent predicted was 9.96% for CIC 40 (p=NS vs. placebo), 10.32% for CIC 80 (p=NS vs. placebo), 12.15% for CIC 160 (p=0.0283 vs. placebo), and 8.61% for placebo. FEV_1 improved significantly from baseline to Week 12 in the CIC 160 group (mean increase 0.28 L, p=0.0118 vs. placebo) but not in the CIC 40 and CIC 80 groups. Increases in AM PEF were statistically

significant from baseline to Week 12 in the CIC 40 treatment group only (mean increase 16.45 L/min, p=0.0369 vs. placebo, 8.66 L/min). All CIC groups demonstrated significant baseline to Week 12 improvement in 24-hour asthma severity rating scores compared with the placebo group (mean decrease for CIC 40, CIC 80, CIC 160 was -0.59, -0.50, and -0.51, respectively, $p<0.004$ for all vs. placebo, placebo decrease was -0.02). The mean number of albuterol puffs per day decreased from baseline to Week 12 in all ciclesonide groups but with statistically significant decreases in the CIC 80 group (-0.42 puffs/day, p=0.0288 vs. placebo) compared to placebo (0.03 puffs/day). All CIC groups resulted in statistically significant improvements in the overall Quality of life (PAQLQ) score from baseline to Week 12 (CIC 40 0.42, p=0.0058 vs. placebo; CIC 80 0.31, p=0.0440 vs. placebo; CIC 160 0.41, p=0.0048 vs. placebo, placebo 0.05).

The incidence of treatment-emergent adverse events was comparable in all four treatment groups (CIC 40 59.7%, CIC 80 61.6%, CIC 160 67.2%, placebo 71.7%). The most common treatment-emergent adverse events that occurred in more than 10% of any patient group were nasopharyngitis (CIC 40 5.4%, CIC 80 13.6%, CIC 160 14.9%, and placebo 8.7%), pharyngitis (CIC 40 10.1%, CIC 80 7.2%, CIC 160 11.2%, and placebo 10.2%), asthma aggravated (CIC 40 9.3%, CIC 80 8.8%, CIC 160 9.7%, and placebo 15.7%), and upper respiratory tract infection (CIC 40 10.1%, CIC 80 10.4%, CIC 160 9.0%, and placebo 13.4%).

Oral candidiasis was reported in 1 (0.8%) CIC 80 patient and 2 (1.5%) CIC 160 patients. Hoarseness was reported in 1 (0.8%) CIC 40 patient with no other reports. Pharyngitis results are listed above.

Lenticular opacity was reported in one patient in the CIC 40 group and one patient in the CIC 80 group. Both of these patients had no lenticular opacity at baseline. There were no reports of glaucoma in this trial.

Changes from baseline in serum cortisol concentration upon cosyntropin stimulation and 24-hour urinary free cortisol concentration were seen in all CIC treatment groups, however, the p values were not determined due to small sample size (cortisol measurements were only done in a subset of patients at certain study sites).

Conclusions:
Refer to the results section.

Pediatric QD Dosing Trials (52-weeks)

Open-label, one-year long-term safety study of ciclesonide MDI (40 mcg, 80 mcg, and 160 mcg QD) as compared to fluticasone dry-powder inhaler (DPI, Flovent®, Rotadisk®, 50 and 100 mcg BID) in children with persistent asthma. Data on File. Study Report 341LT.

Objective:
Establish long-term (1-year) safety of once-daily, morning administration of ciclesonide MDI (40 mcg, 80 mcg and 160 mcg) compared to fluticasone propionate (50 mcg and 100 mcg) twice-daily in children with persistent asthma of all severities.

Study Design and Population:
This was a multicenter (26 U.S. sites), randomized, open-label, long-term (12-month) safety extension of a 12-week double-blind study (Study 341), in 193 children 4 to 11 years of age with mild, moderate, or severe persistent asthma. Patients were included if they had completed or participated in Study 341 for at least 2 weeks. Also, patients who failed to qualify for Study 341 (either couldn't demonstrate a 10% decrease in FEV_1 during screening when previous ICS was discontinued or previously on bronchodilators with an asthma symptom score ≥3, albuterol use ≥2 puffs/day, or PEF variability >20% for at least 3 days during the randomization period) were eligible to participate in this trial. Patients who were active in Study 341 continued their ciclesonide dose after at least 2 weeks.

Patients were randomized to ciclesonide MDI (CIC) or fluticasone propionate dry powder (FDP) in a 2:1 ratio. The daily dose of ciclesonide varied from 40 mcg to 160 mcg (ex-actuator) once-daily in the morning (n = 129) and fluticasone propionate varied from 50 mcg to 100 mcg (ex-valve) twice-daily (n = 64). All patients were randomized to the highest dose of ciclesonide (i.e., 160 mcg/day) or fluticasone propionate (i.e., 200 mcg/day) and were to remain at that dose for at least 2 weeks. After Visit 2, at the investigator's discretion, the dose could be titrated to the lower dose(s) of ciclesonide (i.e., 80 mcg/day or 40 mcg/day) or fluticasone propionate (i.e., 100 mcg/day) as indicated for asthma control. While the patient was at one of the lower doses of study medication, the investigator could choose to return (with no intermediate steps) to the higher dose(s) of ciclesonide (i.e., 80 mcg/day or 160 mcg/day) or fluticasone propionate (i.e., 100 mcg/day), according to the patient's response to treatment. The goal of the dose adjustments was to find the lowest dose that provided effective control of the patient's asthma. Albuterol was provided for use as needed for the relief of acute asthma symptoms throughout the study.

Safety assessments performed included adverse events, clinical laboratory values (including serum cortisol and 24-hour urinary cortisol), physical examinations, vital signs, oropharyngeal examinations, and ophthalmologic examinations.

Results:
The age range was 4-12 years of age with a median age of 8.4 years. The mean FEV_1 percent predicted at baseline was 80.9%.

Overall, treatment-emergent adverse events were reported for 79.8% of patients in the CIC group and for 81.3% of patients in the FDP group. The most common adverse events (reported by >10% of patients in any treatment group) were asthma NOS (CIC 29.5%, FDP 21.9%), nasopharyngitis (CIC 22.5%, FDP 17.2%), upper respiratory tract infection NOS (CIC 14.7%, FDP 21.9%), viral infection NOS (CIC 7.0%, FDP 10.9%), sinusitis NOS (CIC 15.5%, FDP 14.1%), ear infection NOS (CIC 10.9%, FDP 4.7%), pyrexia (CIC 14.0%, FDP 14.1%) and headache (CIC 14.0%, FDP 9.4%). The percentage of patients who did not complete more than 50 weeks of medication was similar between the two groups (CIC 29.5% and FDP 31.2%).

The changes from baseline in mean basal serum cortisol concentrations before low-dose cosyntropin stimulation were minimal and non-significant in both treatment groups [CIC 1.4 mcg/dL (95% CI: -1.9, 4.6) and FDP -1.4 (95% CI: -5.4, 2.6)]. Changes from baseline in 24-hour urinary free cortisol concentrations were minimal and non-significant in both treatment groups [CIC 1.95 mcg/day (SD 5.54) and FDP -1.99 mcg/day (SD 3.60)].

Local oropharyngeal adverse events were reported as follows: oral candidiasis (CIC 0%, FDP 1.6%), pharyngitis (CIC 2.3%, FDP 3.1%), pharyngolaryngeal pain (CIC 5.4%, FDP 7.8%), and hoarseness (0% both groups).

A treatment-emergent lenticular opacity was observed in 3 patients in the CIC group (2.3%). There were no cases of lenticular opacity observed in the FDP group. There were no cases of glaucoma in either treatment group.

In terms of efficacy, asthma control, as measured by FEV_1, improved from baseline to end of study and was maintained throughout the study in both the CIC and the FDP groups.

Conclusions:
Refer to the results section.

Open-label, one-year long-term safety study of ciclesonide MDI (40 mcg, 80 mcg, and 160 mcg QD) as compared to fluticasone dry-powder inhaler (DPI, Flovent®, Rotadisk®, 50 and 100 mcg BID) in children with persistent asthma. Data on File. Study Report 342LT.

Objective:
Establish long-term (1-year) safety of once-daily morning administration of ciclesonide MDI (40 mcg, 80 mcg and 160 mcg) compared to fluticasone propionate twice-daily (50 mcg and 100 mcg) in children with persistent asthma of all severities.

Study Design and Population:
This was a multicenter (26 U.S. sites), randomized, open-label, long-term (12-month) safety extension of a 12-week double-blind study (Study 342), in 190 children 4 to 11 years of age with mild, moderate or severe persistent asthma. Patients were included if they had completed or participated in Study 341 for at least 2 weeks. Also, patients who failed to qualify for Study 341 (either couldn't demonstrate a 10% decrease in FEV_1 during screening when previous ICS was discontinued or previously on bronchodilators with an asthma symptom score ≥3, albuterol use ≥2 puffs/day, or PEF variability >20% for at least 3 days during the randomization period) were eligible to participate in this trial. Patients who were active in Study 342 continued their ciclesonide dose after at least 2 weeks.

Patients were randomized to ciclesonide or fluticasone propionate dry powder inhaler (FDP) in a 2:1 ratio. The daily dose of ciclesonide varied from 40 mcg to 160 mcg (ex-actuator) once-daily in the morning (n = 128) and fluticasone propionate varied from 50 mcg to 100 mcg (ex-valve) twice-daily (n = 62). All patients were randomized to the highest dose of ciclesonide (i.e., 160 mcg/day) or fluticasone priopionate (i.e., 200 mcg/day) and were to remain at that dose for at least 2 weeks. After Visit 2, at the investigator's discretion, the dose could be titrated to the lower dose(s) of ciclesonide (i.e., 80 mcg/day or 40 mcg/day) or fluticasone propionate (i.e., 100 mcg/day) as indicated for asthma control. While the patient was at one of the lower doses of study medication, the investigator could choose to return (with no intermediate steps) to the higher dose(s) of ciclesonide (i.e., 80 mcg/day or 160 mcg/day) or fluticasone propionate (i.e., 100 µg/day), according to the patient's response to treatment. The goal of the dose adjustments was to find the lowest dose that provided effective control of the patient's asthma. Albuterol was provided for use as needed for the relief of acute asthma symptoms throughout the study.

Safety assessments performed included: adverse events, clinical laboratory values (including serum cortisol and 24-hour urinary cortisol), physical examinations, vital signs, oropharyngeal examinations, and ophthalmologic examinations.

Results:
The age range was 4-12 years of age with a mean age of 8.6 years of age. The mean FEV_1 percent predicted at baseline was 79.5%.

Overall, treatment-emergent adverse events were reported for 85.9% of patients in the CIC group and 73.8% of patients in the FDP group. The most common treatment-emergent adverse events (reported by >10% of patients in any treatment group) were asthma NOS (CIC 32.8%, FDP 16.4%), nasopharyngitis (CIC 25.0%, FDP 16.4%), upper respiratory tract infection NOS (CIC 26.6%, FDP 16.4%), sinusitis NOS (CIC 10.2%, FDP 18.0%), otitis media NOS (CIC 10.2%, FDP 3.3%), pyrexia (CIC 15.6%, FDP 11.5%) and headache (CIC 14.1%, FDP 14.8%). There was a greater percentage of patients who permanently discontinued the trial in the CIC group (CIC 8.6% and FDP 1.6%). The percentage of patients who did not complete more than 50 weeks of medication was similar between the two groups (CIC 27.3% and FDP 30.6%).

Very few patients had data available for serum or urinary free cortisol analyses. Of the data that was collected, there were no meaningful differences between baseline and end of study basal or 24-hour urinary free cortisol concentrations.

Local oropharyngeal adverse events were reported as follows: oral candidiasis (CIC 1.6%, FDP 3.3%), pharyngitis (CIC 0.8%, FDP 0.0%), pharyngolaryngeal pain (CIC 9.4%, FDP 8.2%) and hoarseness (0% in both groups).

There were no patients in the CIC group and one patient in the FDP group who had treatment-emergent lenticular opacity at the follow-up exam. One CIC patient was diagnosed with low-tension glaucoma during the treatment period.

In terms of efficacy, asthma control, as measured by FEV_1, improved from baseline to end of study and was maintained throughout the study in both the CIC and the FDP groups.

Conclusions:
Refer to the results section.

Pediatric Growth Trial (52-weeks in Duration)

Skoner D, Maspero J, Banerji D and the Ciclesonide Pediatric Growth Study Group. Assessment of the long-term safety of inhaled ciclesonide on growth in children with asthma. *Pediatrics.* 2008;121(1): e-publication (e1-e14). Study Report 343.

Objective:
Assess the effects of ciclesonide on growth in children with asthma

Study Design and Population:
A multi-center, randomized, double-blind, placebo-controlled, non-inferiority trial in children (aged 5 to 8.5 years) with mild persistent asthma evaluated the long-term (52-weeks) effects of orally-inhaled ciclesonide on growth velocity. Patients were recruited from a total of 85 sites in the U.S. and South America. Patients were required to have a history of mild persistent asthma for at least 3 months prior to Visit 1, a FEV_1 of ≥80% of predicted following at least a 4-hour albuterol withhold, and treated with non-corticosteroid asthma medications on an as-needed or daily basis, or with low doses of inhaled corticosteroids (ICS) for at least one month prior to Visit 1. Patients were to be classified in Stage 1 or less in the Tanner classification of sexual maturity.

The trial consisted of 3 phases: a 6-month run-in period in which albuterol was used to control asthma symptoms, a 52-week double-blind treatment period in which children were randomized to receive treatment with ciclesonide 40 mcg (n = 221), ciclesonide 160 mcg (n = 219), or placebo (n = 221) once daily in the morning via hydrofluoroalkane MDI, and a 2-month follow-up period.

The primary end point in this trial was growth velocity during the double-blind treatment period, whereby height measurements were assessed via Harpenden stadiometers at each clinic visit. As a secondary endpoint, bone age was determined using wrist radiographs. Treatment-emergent adverse events, including oropharyngeal events, were monitored throughout the trial. Urine samples were also collected to assess cortisol measurements.

Results:
The age range was 5 to 8.6 years of age with a mean age of 6.7 years. The mean FEV_1 percent predicted range was 96.0% to 96.2%. The mean range in stadiometric height at randomization was 122.6 cm to 123.4 cm. Wrist x-ray assessments at randomization identified 48.1% and 33.3% of all patients with high bone age and normal bone age, respectively.

Mean growth velocity at the run-in period was slightly lower in the ciclesonide 160 mcg treatment group (6.20 cm/year) compared with the other groups (6.59 cm/year and 6.49 cm/year for ciclesonide 40 mcg and placebo, respectively). Overall growth rates were lower during the double-blind treatment period compared with the run-in and follow-up periods. Mean differences from placebo (5.75 cm/year) in growth velocity over the double-blind treatment period were -0.02 cm/year for ciclesonide 40 mcg and -0.15 cm/year for ciclesonide 160 mcg ($p=0.0001$ for both ciclesonide groups vs placebo indicating non-inferiority). The shift in chronologic age relative to bone age range from

baseline to the end of the study was comparable among the treatment groups. A high ratio of chronological age to bone age is indicative of growth retardation. There were only 17 subjects with shifts from a normal or low ratio to a high ratio between the run-in and double-blind treatment periods with higher frequencies of these shifts occurring in the placebo (7 patients, 4.0%) or ciclesonide 40 mcg (8 patients, 4.3% groups than in the ciclesonide 160 mcg group (2 subjects, 1.1%).

Treatment-emergent adverse events occurred in 94.6%, 90.0% and 89.6% of patients in the CIC 80 mcg, CIC 160 mcg, and placebo groups, respectively. The most common treatment-emergent adverse event in ≥10% of patients in any group (CIC 40 mcg, CIC 160 mcg, and placebo) were asthma (33.5%, 29.7%, and 33.9%), nasopharyngitis (31.7%, 31.1%, and 26.2%), pyrexia (28.1%, 20.1%, and 19.9%), headache (18.6%, 19.6%, and 18.1%), upper respiratory infection (14.0%, 12.8%, and 11.8%), influenza (13.1%, 10.0%, and 9.0%), bronchitis (10.4%, 10.0%, and 10.0%), rhinitis (10.0%, 5.9%, and 9.5%), and pharyngitis (see below).

The incidence of local oropharyngeal adverse events were comparable in the CIC 40 mcg, CIC 160 mcg, and placebo groups: oral candidiasis, 0%, 0%, and 0.5%; pharyngolaryngeal pain, 3.6%, 4.1%, and 3.6%; pharyngitis, 16.3%, 12.8%, and 15.4%; and hoarseness, 0% in all groups.

The change from baseline to the end of the double-blind treatment period in 24-hour urinary free cortisol (corrected for creatinine) was -0.002 mcg/mg, -0.003 mcg/mg, and -0.002 mcg/mg for the CIC 40 mcg, CIC 160 mcg and placebo groups, respectively (p=NS for either CIC group versus placebo).

Conclusion:
Conclusions cannot be drawn from this trial since compliance could not be confirmed (not sure if patients took their ciclesonide inhaler as directed), blood levels were not measured and no difference in efficacy measures between the placebo and ciclesonide treatment groups were seen.

Pediatric Trial of Twice-daily Ciclesonide vs. Fluticasone propionate

Pedersen S, Garcia ML, Manjra A, Theron I, Engelstatter R. A comparative study of inhaled ciclesonide 160 µg/day with fluticasone propionate 176 µg/day in children with asthma. *Pediatr Pulmonol*. 2006. 41:954-961. Clinical Study Report 54/2003.

Objective:
To compare the safety and efficacy of ciclesonide 80 mcg twice daily with that of fluticasone propionate 88 mcg twice daily for 12 weeks in children and adolescents with persistent asthma.

Study Design and Population:
This was a 12-week, multicenter, randomized, double-blind, double-dummy, parallel-group non-inferiority study. Patients between the ages of 6 and 15 years with persistent asthma as defined by the ATS for at least 6 months were eligible to participate. Enrollment occurred in 51 sites in Canada, Europe and South Africa. Patients were required to be clinically stable for 4 weeks before screening without any need for treatment adjustment. At the beginning of the baseline period, FEV_1 percent predicted had to be between 50% and 90% for patients currently on rescue medication only, between 80% and 100% predicted for patients treated with inhaled corticosteroids for at least 30 days before screening, and between 50% and 100% predicted for patients taking other controller asthma medications (but not inhaled corticosteroids). Patients were randomized to receive HFA MDI formulations of ciclesonide 80 mcg (ex-actuator) twice-daily (n = 277) or fluticasone propionate 88 mcg (ex-actuator) twice-daily (n = 279) for 12 weeks.

The primary efficacy endpoint was the change in FEV_1 from baseline to Week 12. Co-primary efficacy endpoints included the change in morning and evening PEF. Secondary endpoints included asthma symptom scores rescue medication use (salbutamol) from randomization to the end of treatment. Treatment-emergent adverse events were monitored throughout the trial. Collection of 24-hour urine samples for analysis of free urine cortisol and creatinine occurred during week 2 of the baseline period and at the end of treatment.

Results:
The mean age of patients was 10 years of age (range, 6 to 16 years). The mean FEV_1 percent predicted at baseline was 80%.

FEV_1 improved by 0.285 L in the CIC and FP treatment groups ($p<0.0001$ for both groups vs. baseline). The between-treatment LS mean difference between CIC and FP was 0.000 with a two-sided p-value of 0.9855, demonstrating non-inferiority of CIC compared to FP. Statistically significant increases from baseline to Week 12 ($p<0.0001$ for both treatment groups) in AM PEF (30.8 L/min for CIC, 33.7 L/min for FP) were observed in both treatment groups, with no statistically significant difference between groups. Comparable results were demonstrated for PM PEF ($p<0.0001$ vs. baseline for both treatment groups, no statistically significant differences between CIC and FP). Median total asthma symptom scores improved from 1.43 to 0.00 in the CIC group and

1.29 to 0.00 in the FP treatment group ($p<0.0001$ for both groups). Rescue medication use was similar in the two treatment groups (median was 0 puffs/day for both groups at study endpoint). For both the changes in asthma symptoms scores and rescue medication use, the difference between CIC and FP was not statistically significant.

A similar percentage of treatment-emergent adverse events occurred in both treatment groups (CIC 35.7% and FP 33.0%). The most commonly reported adverse events occurring in 3% or more of the patients in either treatment group were rhinitis (CIC 7.9%, FP 8.2%), upper respiratory tract infection (CIC 6.9%, FP 6.5%), pharyngitis (CIC 4.3%, FP 3.9%), asthma (CIC 3.6%, FP 2.9%), headache (CIC 3.6%, FP 2.5%), and sinusitis (CIC 1.8%, FP 3.2%).

The incidence of oropharyngeal adverse events such as sore throat (CIC 1.4%, FP 0.7%), pharyngitis (CIC 4.3%, FP 3.9%), voice alteration (CIC 0%, FP 0.4%), and oral candidiasis (CIC 0%, FP 0.7%) was low and similar in both treatment groups.

The 24-hour free urine cortisol adjusted for creatinine increased from baseline to treatment endpoint in both treatment groups with a significant increase occurring only in the CIC group (LS mean difference +2.361 nmol/mmol creatinine, $p=0.040$). The difference between the treatment groups was not statistically significant.

Conclusions:
Refer to the results section.

Pediatric Trial of Once-daily Ciclesonide vs. Budesonide

von Berg A, Engelstätter R, Minic P, et al. Comparison of the efficacy and safety of ciclesonide 160 µg once daily vs. budesonide 400 µg once daily in children with asthma. *Pediatr Allergy Immunol*. 2007:18:391–400. Clinical Study Report 278/2004.

Objective:
To compare the safety, efficacy, and effect on quality of life of ciclesonide 160 mcg once-daily in the evening versus budesonide 400 mcg once-daily in the evening in children with persistent asthma.

Study Design and Population:
This was a multicenter (59 centers, 8 non-US countries [European Union, Australia, South Africa]), randomized, double-blind, double-dummy, two-arm, parallel-group non-inferiority study. Patients aged 6 to 11 years with a documented diagnosis of persistent asthma (per GINA guidelines) for at least 6 months were eligible to participate in this study. Patients were required to have a FEV_1 of 50% to 90% of predicted in patients receiving rescue medication only, 50% to 100% of predicted in patients pretreated with a constant dose of controller medication other than steroids for at least 30 days before inclusion, or 80% to 105% of predicted in patients pretreated with ≤400 mcg/day beclomethasone or equivalent for at least 30 days before inclusion. To be eligible for randomization, patients were required to have an FEV_1 of 50% to 90% of predicted after withholding salbutamol for at least 4 hours, reversibility of FEV_1 ≥12% of initial after inhalation of salbutamol 200-400 mcg, and asthma symptom scores ≥1 on at least six of the previous 10 consecutive days or use of ≥8 puffs of rescue medication during the previous 10 consecutive days. Patients underwent a 2 to 4 week run-in period during which they discontinued their previous asthma medication and received only salbutamol as rescue medication. Eligible patients were randomized in a 2:1 ratio to receive HFA MDI formulations of ciclesonide 160 mcg (ex-actuator) once-daily in the evening (CIC QD_{PM}, n = 416) or budesonide 400 mcg (ex-valve) once daily administered in the evening (BUD QD_{PM} n = 205) for 12 weeks.

The primary efficacy endpoint was the change in FEV_1 after 12 weeks of treatment (per protocol analysis). Secondary endpoints included changes from baseline to Week 12 for morning PEF, asthma symptom scores, rescue medication use, and quality of life questionnaire scores (PAQLQS and PACQLQ). Treatment-emergent adverse events were monitored throughout the trial. In addition, body height (assessed by stadiometry) and changes in 24-hour urinary cortisol adjusted for creatinine was measured from baseline to Week 12.

Results:
The mean age of patients in this trial was 9 years of age (range 6-11 years of age). The mean FEV_1 percent predicted at baseline was between 77% and 78%.

Treatment with CIC QD_{PM} and BUD QD_{PM} achieved statistically significant increases in FEV_1 after 12 weeks of treatment (0.220 L and 0.253 L per protocol analysis (PP), $p<0.0001$ for both treatment groups vs. baseline; 0.232 L and 0.250 L intent-to-treat

analysis (ITT), p<0.0001 for both treatment groups vs. baseline). Non-inferiority of CIC versus BUD was demonstrated for FEV_1 (p=0.0009 for CIC non-inferiority PP; p<0.0001 for CIC non-inferiority ITT). Treatment with CIC and BUD achieved statistically significant increases in morning PEF after 12 weeks of treatment (22.5 L/min and 26.3 L/min, p<0.0001 vs. baseline, PP; 22.7 L/min and 25.0 L/min, p<0.0001 vs baseline, ITT). Both the CIC and BUD groups achieved statistically significant improvements in asthma symptom score sum after 12 weeks of treatment (-1.21 for both, PP; -1.18 and -1.19, respectively, ITT, p<0.0001 versus baseline for both groups, both analyses). Both the CIC and BUD groups achieved a statistically significant reduction in the need for rescue medication after 12 weeks of treatment (-1.64 puffs/day for both, PP; -1.58 and -1.64 puffs/day ITT, respectively, p<0.0001 vs. baseline for both groups, both analyses). The difference between treatment groups for changes in asthma symptom scores and rescue medication use was not statistically significant. Both treatment groups achieved statistically significant improvements in overall scores versus baseline on the PAQLQ(S) and PACQLQ (CIC 0.73 and 0.92, BUD 0.74 and 0.98, PP; CIC 0.69 and 0.88, BUD 0.70 and 0.96, ITT; all p<0.0001 for both analyses). Non-inferiority of CIC versus BUD was demonstrated in the PAQLQ(S) and PACQLQ (ITT, p<0.5738).

Treatment-emergent adverse events occurred in approximately 38% of patients in both treatment groups. The following treatment-emergent adverse events occurred in 3% or more of patients in either group: asthma aggravated (CIC 4.1%, BUD 1.0%), pharyngitis (CIC 6.0%, BUD 6.8%), nasopharyngitis (CIC 4.1%, BUD 5.4%), and upper respiratory tract infection (CIC 3.6%, BUD 6.3%).

The frequency of patients reporting oropharyngeal adverse events, including oral candidiasis and dysphonia, was low in both groups (CIC 0.2%, BUD 1.5%).

Body height increased by 1.18 cm and 0.70 cm in the CIC and BUD groups, respectively, after 12 weeks of treatment (both p<0.0001 versus baseline). The increase in body height was significantly greater in CIC patients than in BUD patients (p=0.0025).

After 12 weeks, treatment with CIC and BUD resulted in statistically significant decreases (-2.17 [-6.9%] and -5.16 [-22.9%] nmol/mmol creatinine) in 24-hour urinary cortisol adjusted for creatinine (both p<0.0001 versus baseline). The decrease in 24-hour urinary cortisol was significantly greater in the BUD group compared with the CIC group (p<0.0001).

Conclusions:
Refer to the results section.

Other Pediatric Trials

The following table lists other references that provide published clinical data regarding inhaled ciclesonide in the pediatric population. This list is not meant to be all-inclusive.

Reference	Treatment Arms*	Duration	Population
Agertoft L, Pedersen S. Short-term lower-leg growth rate and urine cortisol excretion in children treated with ciclesonide. *J Allergy Clin Immunol.* 2005;115:940-945.	-CIC 40, 80, 160 mcg QD_{PM} -Placebo	Cross-over, each arm 2 weeks	N=24 6-12 years of age
Hiremath L, Mohan-Kumar T, Singh V, Raman P, Ramsperger U, Engelstatter R. Comparison of once-daily ciclesonide 160 µg versus twice-daily fluticasone propionate 88 µg in children with moderate to severe asthma [abstract]. *Eur Respir J.* 2006;28(Suppl. 50):711s.	-CIC 160 mcg QD_{PM} -FP 88 mcg BID	12 weeks	N=512 4-15 years of age
Pedersen S, Cruz AA, Fiterman J, Barkai L, Hirsch S, Engelstatter R. Comparison of ciclesonide once daily (80 µg/d, 160 µg/d) and fluticasone propionate twice daily (176 µg/d) in the treatment of children with persistent asthma [abstract]. *Eur Respir J.* 2007;30(Suppl. 51):458s.	-CIC 80, 160 mcg QD -FP 88 mcg BID	12 weeks	N=744 6-11 years of age
Agertoft L, Pedersen S. Comparison of lower leg growth rate in prepubertal children with mild asthma treated with inhaled placebo, ciclesonide, or fluticasone propionate [abstract]. *Allergy.* 2007;62(Suppl. 83):131.	-CIC 160 mcg BID -FP 250 mcg AM and 125 mcg PM (ex-valve) -Placebo	Cross-over, each arm 2 weeks	N=28 6-12 years of age
Meltzer EO, Sotomayor JL, Kundu S, Banerji D. Long-term safety profile of once-daily ciclesonide in children with persistent asthma of all severities [abstract]. *Ann Allergy Asthma Immunol.* 2006;96:140-141.	-CIC 160 mcg QD_{AM} for 2 weeks then titrated to CIC 40, 80, or 160 mcg QD_{AM} as needed to maintain asthma control -FP 100 mcg BID (ex-valve) for 2 weeks then titrated to FP 50 or 100 mcg BID as needed to maintain asthma control	52 weeks	N=615 4-11 years of age

* Doses ex-actuator unless otherwise specified
CIC-ciclesonide, FP- fluticasone propionate

Evidence Tables

Table E.1 Evidence Table Spreadsheet for Ciclesonide in the Treatment of Mild to Moderate Persistent Asthma in Adults Previously Maintained on Bronchodilators

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
3031	Phase III, MC, R, DB, PCO, PG, multi-national	• CIC 80 mcg BID • CIC 160 mcg QD_{AM} • CIC 80 mcg BID for 4 wks, then 160 mcg QD_{AM} for 12 wks • Placebo	691	16 weeks	Inclusion: • ≥12 years of age • History of persistent asthma for ≥6 months prior to screening • After SABA withhold of 6 hours: FEV_1 of 60% to 85% • Therapy limited to bronchodilators only in 1 month prior to screening	Primary: AM pre-dose FEV_1 Secondary: • AM PEF • Albuterol use • Asthma symptom score • Treatment-emergent adverse events	*Results*: • Patient age: 11-73, median 35 to 39 years. • Mean FEV_1 percent predicted at baseline was 72.0%. • All active treatments showed significant improvement in AM pre-dose FEV_1 compared to placebo in the change from baseline to the average of Weeks 12 and 16 [BID- 0.24 L (p<0.0001), QD- 0.12 L (p=0.0021), BID to QD- 0.13 L (p=0.0016)]. • All treatment groups significantly improved AM PEF [BID- 36.16 L/min (p<0.0001), QD- 23.32 L/min (p=0.0006), BID to QD- 30.71 L/min (p<0.0001)] and decreased albuterol use [BID -0.73 puffs/day (p<0.0001), QD -0.41 puffs/day (p=0.0116), BID to QD -0.60 puffs/day (p=0.0002)]. • The total asthma symptom score was significantly improved in the BID and BID to QD treatment groups but not in the QD treatment group. • The incidence of AEs was similar among groups (BID- 55.5%, QD- 52.8%, BID to QD- 57.8%, placebo- 57.3%). • Adverse events occurring in at least 3% of patients for BID, QD, BID to QD, and placebo groups were asthma 5.2%, 8.0%, 10.4% and 14%; nasopharyngitis 11.6%, 10.8%, 5.2% and 9.6%; headache 5.8%, 9.1%, 8.7% and 7.9%; upper respiratory tract infection 5.2%, 3.4%, 7.5% and 6.2%; influenza 3.5%, 4.5%, 3.5% and 1.7%; pharyngolaryngeal pain 2.9%, 2.8%, 2.3% and 4.5%; back pain 0.6%, 1.1%, 3.5% and 1.7%; and sinusitis 2.9%, 4.0%, 3.5% and 1.7%. • A higher percentage of patients permanently discontinued study medication due to a treatment-emergent adverse event in the placebo group (12.4%) compared to the CIC QD, BID to QD, and BID groups (8.0%, 4.6%, and 2.3%). • The incidence of oropharyngeal adverse events was similar between the treatment groups (for BID, QD, BID to QD, and placebo groups: pharyngolaryngeal pain 2.9%, 2.8%, 2.3% and 4.5%; pharyngitis 2.9%, 0.6%, 1.7%, and 0.6%; and dysphonia 0%, 0.6%, 0%, and 0.6%). There were no cases of oral candidiasis. *Conclusion:* In this trial ciclesonide was effective compared to placebo in patients with mild to moderate asthma previously treated with inhaled bronchodilators alone and was well-tolerated compared to placebo.

MC=multicenter, R=randomized, DB=double-blind, PCO=placebo-controlled, PG=parallel-group, PEF=Peak expiratory flow, SABA=short-acting beta-agonist, FEV_1=forced expiratory volume in 1 second, CIC=ciclesonide

Table E.2 Evidence Table Spreadsheet for Ciclesonide in the Treatment of Mild to Moderate Persistent Asthma in Adults Previously Maintained on Inhaled Corticosteroids

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
3030	Phase III, MC, R, DB, PCO	• CIC 80 mcg BID • CIC 160 mcg QD_{AM} • Placebo	456	12 weeks	Inclusion: • ≥12 years of age • History of persistent asthma for ≥6 months prior to screening • Documented use of ICS or ICS/LABA combination medication for at least 1 month prior to screening • FEV_1 of 60% to 90% (ICS) or 70% to 95% (ICS/LABA) of predicted normal at baseline • Continuation of ICS (≤440 mcg/day FP or equivalent) or ICS/LABA (≤200/100 mcg/day FP/salmeterol) during screening	Primary: AM pre-dose FEV_1 Secondary: • AM PEF • Albuterol use • Total asthma symptom score • Treatment-emergent adverse events	*Results*: • Patient age: 12 and 79 years of age with a median age range of 37 to 44 years. • The mean FEV_1 percent predicted at baseline was approximately 79%. • Both active treatments showed significant improvement in AM pre-dose FEV_1 compared to placebo in the change from baseline to Week 12 [BID- 0.19 L (p<0.0001), QD- 0.14 L (p=0.0006)]. • Compared to the placebo group, there was statistically significant improvement in AM PEF for the CIC BID group but not for the CIC QD group. • Significant decrease in albuterol use occurred in the CIC BID and QD groups (-0.64 puffs/day, p<0.0001 and -0.60 puffs/day, p=0.0002, respectively). • The total asthma symptom score similarly improved in both CIC BID and QD groups (-0.37, p=0.0011 and -0.38, p=0.0010, respectively). • The incidence of adverse events was similar among groups (BID- 52%, QD- 57.9%, placebo- 55.3%). • Adverse events occurring in at least 2% of patients in CIC BID, CIC QD, or placebo groups were nasopharyngitis (9.2%, 12.5%, 5.9%), upper respiratory tract infection (9.2%, 7.9%, 7.9%), pharyngolaryngeal pain (5.9%, 5.3% , 3.3%), sinusitis (3.3%, 5.9%, 4.6%), asthma (3.3%, 4.6%, 17.8%), headache (3.9%, 3.9%, 3.9%), cough (2.0%, 5.3%, 2.0%), gastroenteritis viral (0.7%, 3.9%, 1.3%) and toothache (0%, 3.3%, 1.3%). • A higher percentage of patients permanently discontinued study medication due to a treatment-emergent adverse event in the placebo group (15.8%) compared to the CIC BID and CIC QD groups (5.3% and 4.6%, respectively). • The incidence of oropharyngeal adverse events was similar between the treatment groups (for BID, QD, and placebo groups: pharyngolaryngeal pain 5.9%, 5.3%, and 3.3%; pharyngitis 0%, 1.3%, and 0%; dysphonia 0%, 0%, and 0.7%); and oral candidiasis (0.7%, 0%, and 0%). *Conclusion*: In this trial, ciclesonide administrated at a daily dose of 160 mcg as 80 mcg BID is effective compared to placebo in patients with mild to moderate asthma is effective. The data demonstrated that this dose was well-tolerated compared to placebo.

MC=multicenter, R=randomized, DB=double-blind, PCO=placebo-controlled, ICS=inhaled corticosteroid, LABA=long-acting beta-agonist, FP=fluticasone propionate, FEV_1=forced expiratory volume in 1 second, PEF=peak expiratory flow, CIC=ciclesonide, BID=twice daily, QD=once daily, AM=morning

Table E.3 Evidence Table Spreadsheet for Ciclesonide in the Treatment of Moderate to Severe Persistent Asthma in Adults Previously Maintained on Inhaled Corticosteroids

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
323/324	Phase III, MC, R, DB, PCO, parallel group, active-controlled	• CIC 160 mcg BID • CIC 320 mcg BID • FP 440 mcg BID • Placebo	531	12 weeks	Inclusion: • ≥12 years of age • History of persistent asthma for ≥1 year prior to screening • Documented use of ICS (FP or MOM ≥500mcg/day or BUD, BDP, FLU, TRI ≥800mcg/day) for the month prior to screening • Beta-agonist use more than 2 times a week for the month prior to screening • Patients were required to have at least a one year history of persistent asthma, an FEV_1 of 80% or less of predicted normal following a six-hour beta-agonist treatment withholding period at screening, and an FEV_1 between 40% and 65% of predicted normal following a six-hour beta-agonist treatment withholding	Primary: Change from baseline to Week 12 in AM pre-dose FEV_1 compared to placebo Secondary: • AM PEF • Albuterol use • Total asthma symptom score • AQLQ • Treatment-emergent adverse events	*Results*: • Patient age: 12 and 88 years of age with a mean age range of 42 to 44 years. • The mean FEV_1 percent predicted at baseline was approximately 53.7%. • All active treatments showed an improvement in AM pre-dose FEV_1 from baseline to Week 12 compared to placebo (CIC 160 mcg- 0.11, p= 0.0374, CIC 320 mcg- 0.18, p= 0.0008, FP- 0.24, p= 0.0001) • Improvements in morning peak expiratory flow, albuterol use, and total asthma symptoms scores were significant in both of the CIC treatment groups and the FP group (p=0.0001). • All four measures in the AQLQ (overall score, symptoms, activity limitation, and emotional function) were statistically significantly improved in both CIC treatment groups and FP treatment group compared to placebo from baseline to Week 12. • The percentage of patients who achieved the minimally important difference (MID) for improvement in the AQLQ Overall Score (an increase of at least 0.5) at Week 12 were 42.5% in the CIC 160 mcg BID group, 43.1% in the CIC 320 mcg BID group, and 58.8% in the FP treatment group compared with 26.9% in the placebo group. • The percentage of patients with treatment-emergent adverse events for all three of the active groups was comparable to the placebo group with treatment-emergent adverse events occurring in 61.4% of CIC 160 mcg BID patients, 54.6% of CIC 320 mcg BID patients, 60.1% of FP patients, and 61.8% of placebo patients. • A higher percentage of patients permanently discontinued study medication in the placebo group (19.9%) compared to CIC 160 mcg BID, 320 mcg BID and FP treatment groups (6.3%, 7.7% and 4.3%). • Treatment emergent adverse events reported by at least 10% of patients in any of the treatment groups (CIC 160 mcg BID, CIC 320 mcg BID, FP and placebo) included asthma aggravated (7.9%, 10.8%, 2.2% and 19.9%, respectively), nasopharyngitis (10.2%, 6.9%, 10.9% and 7.4%), and oral candidiasis (1.6%, 0%, 11.6% and 2.2%). • Oropharyngeal adverse events were more common in the FP group compared to the ciclesonide groups or placebo (for CIC 160 mcg BID, CIC 320 mcg BID, FP and placebo groups: oral candidiasis 1.6%, 0%, 11.6% and 2.2%; pharyngitis 4.7%, 3.1%, 5.1%, and 2.9%; and dysphonia 0%, 1.5%, 3.6%, and 0.7%). *Conclusion*: In this trial, daily doses of ciclesonide (160 mcg BID and 320 mcg BID) and fluticasone propionate (440 mcg BID) were effective compared to placebo in the treatment of adolescent and adult patients with moderate to severe persistent asthma. Findings support that 160 mcg BID and 320 mcg BID doses of ciclesonide are safe and effective for the maintenance treatment of moderate to severe persistent asthma as prophylactic therapy.

MC=multicenter, R=randomized, DB=double-blind, PCO=placebo-controlled, ICS=inhaled corticosteroid, FP=fluticasone propionate, MOM=mometasone, BUD=budesonide, BDP=beclomethasone, FLU=flunisolide, TRI=triamcinolone, FEV_1=forced expiratory volume in 1 second, QOL=quality of life, PEF=peak expiratory flow, AQLQ=Asthma Quality of Life Questionnaire, CIC=ciclesonide, AM=morning, BID=twice daily

Table E.4 Evidence Table Spreadsheet for Pivotal Trials For Ciclesonide in the Treatment Severe Persistent Asthma in Adults Maintained on Oral Corticosteroids

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
325; Bateman et al, 2006	Phase III, MC, R, DB, PCO, parallel group	• CIC 320 mcg BID • CIC 640 mcg BID • Placebo	141	12 weeks	Inclusion: • ≥12 years of age • At least one year history of persistent asthma • Corticosteroid dependent, severe asthma • A regimen of oral prednisone at least QOD for 5 of 6 months prior to screening • Failure to completely eliminate prednisone • History of ICS during the 6 months prior to screening with a stable dose used the month immediately prior to screening • Required use of an inhaled beta-agonist for asthma control within the two weeks prior to screening • FEV_1 between 40% and 80% of predicted normal after a 6-hour beta-agonist withholding period.	Primary: Percent change or oral prednisone dose from baseline to end of trial compared to placebo Secondary: • Percentage of patients who were able to completely discontinue predisone use • Changes in respiratory parameters (percent change in baseline AM pre-dose FEV_1 and change in AM PEF • Albuterol use • Total asthma symptom score • Assessment of HPA-axis suppression • Treatment-emergent adverse events	*Results*: • Patient age: Between 12 and 74 years of age with a median age of 48.3 years. • The mean FEV_1 percent predicted at baseline was 53%. • The average prednisone dose at baseline was approximately 12 mg/day. • The percent reduction from baseline to Week 12 in prednisone dose was 4.21% in placebo patients, indicating an increase in prednisone usage during the double-blind period. • The percent reduction in prednisone dose for the CIC 320 mcg BID group was -47.39% ($p = 0.0003$ vs. placebo) and for the CIC 640 mcg BID group was -62.54% ($p = 0.0001$ vs. placebo), with differences being not statistically significant between the two ciclesonide treatment groups ($p=0.274$). • The difference in the LS mean change in prednisone dose from baseline to Week 12 was statistically significantly greater in the CIC treatment groups compared to placebo (CIC 320 mcg- $p=0.0008$; CIC 640 mcg- $p=0.0001$). • At Week 12, the percentage of patients that were able to completely discontinue oral prednisone usage was statistically significantly greater for patients in the CIC groups compared to the placebo group (CIC 320 mcg- 29.8%, $p=0.0386$; CIC 640 mcg- 31.3%, $p=0.0233$; placebo- 11.1%). • Coincident with the reduction in prednisone dose, patients in the CIC group maintained asthma control as evidenced by AM pre-dose FEV_1 (CIC 320 mcg- $p=0.0237$; CIC 640 mcg- $p=0.0277$). • Differences in AM PEF, albuterol use, and asthma symptom scores were not significant in the treatment groups compared to the placebo group. • A higher percentage of patients permanently discontinued study medication in the placebo group (26.7%) compared to the CIC 320 mcg BID and 640 mcg BID groups (14.9% and 8.2%, respectively). • The overall incidence of treatment-emergent adverse events were similar among the treatment groups (CIC 320 mcg BID: 85.1%, CIC 640 mcg BID: 79.6%, and placebo: 88.9%). The most common adverse events that occurred in 10% or more of patients in any treatment group (CIC 320 mcg BID, CIC 640 mcg BID, and placebo) were asthma aggravated (40.4%, 28.6%, and 62.2%), upper respiratory tract infection NOS (19.1%, 18.4%, and 20.0%), headache (14.9%, 12.2%, and 8.9%), sinusitis NOS (10.6%, 12.2%, and 4.4%), nasopharyngitis (6.4%, 12.2%, and 8.9%), arthralgia (0%, 14.3%, and 2.2%), vomiting NOS (0%, 4.1%, and 13.3%), oral candidiasis, and pharyngitis. • The incidence rates of oropharyngeal adverse events for the CIC 320 mcg BID, CIC 640 mcg BID and placebo groups were as follows: oral candidiasis- 6.4%, 12.2%, and 0%, dysphonia- 6.4%, 0%, and 2.2%, and pharyngitis- 6.4%, 4.1%, and 13.3%. • At baseline, 66.0% of patients in the ciclesonide 320 mcg BID group, 60.4% in the ciclesonide 640 mcg BID group, and 62.2% of patients in the placebo group had suppressed (non-normal) HPA-axis function. At Week 12, a smaller proportion of patients in both ciclesonide treatment groups had suppressed (non-normal) HPA-axis function compared with placebo (CIC 320 mcg BID- 46.8%; CIC 640 mcg BID- 43.8% and placebo- 53.3%).

Table E.4 Evidence Table Spreadsheet for Pivotal Trials For Ciclesonide in the Treatment Severe Persistent Asthma in Adults Maintained on Oral Corticosteroids (cont.)

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
							Conclusion: In this trial, in patients with severe persistent asthma who require oral corticosteroids for asthma control, ciclesonide in doses of 320 or 640 mcg given twice daily was an effective and safe alternative to oral corticosteroids. Ciclesonide may permit a reduction or complete elimination of the requirement for oral corticosteroids over time in comparison to placebo. The highest recommended dose of ALVESCO Inhalation Aerosol is 320 mcg BID.

MC=multicenter, R=randomized, DB=double-blind, PCO=placebo-controlled, PEF=Peak expiratory flow, ICS=inhaled corticosteroid, FEV_1=forced expiratory volume in 1 second, PEF=peak expiratory flow, CIC=ciclesonide, AM=morning, BID=twice daily, NOS=not otherwise specified

Table E.5 Evidence Table Spreadsheet for Pivotal Trials For Ciclesonide Long-Term Safety

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
323/324 LT	Phase III, MC, R, DB	• CIC 160 mcg or 320 mcg BID • BDP 160 mcg or 320 mcg BID	297	12 months	Inclusion: • ≥12 years of age • Previous inclusion in study 323/324 and either completion of the trial or at least 2 weeks of double-blind treatment • Patients who failed randomization for study 323/324 who could not demonstrate at least a 10% drop in FEV_1 from screening to randomization and who could not tolerate discontinuation of their LABA during baseline period • Ability to effectively use MDI device	Primary: Safety including: • Adverse events • Serum and urinary cortisol concentrations • Oropharyngeal examinations • Ophthalmologic examinations Secondary: • Pulmonary function tests (FEV_1, FVC)	*Results*: • Patients were between 12 and 76 years of age. • Mean FEV_1 at baseline was 64.8%. • Frequency of treatment-emergent adverse events was comparable across treatment groups (CIC 74.1%, BDP 79.2%). • The most common treatment-emergent adverse events reports (>10% of patients in any treatment group) were: asthma NOS (CIC 18.8%, BDP 18.8%), nasopharyngitis (CIC 14.2%, 19.8%), sinusitis (CIC 13.7%, BDP 6.3%), upper respiratory tract infection (CIC 11.2%, BDP 17.7%), headache (CIC 9.6%, BDP 15.6%), and oral candidiasis. • The incidences of oropharyngeal adverse events were as follows: pharyngolaryngeal pain, CIC 3.0% and BDP 5.2%; oral candidiasis, CIC 4.1% and BDP 10.4%; pharyngitis, CIC 0.5% and BDP 0%; and dysphonia, CIC 2.5% and BDP 1.0%. • Lenticular opacities (cataracts) were reporterd in 9 patients at the end of study who had normal lenses at baseline: 6 patients (3.0%) received CIC, 2 patients (2.1%) received BDP, and one patient received both CIC and BDP. Glaucoma was reported in 2 patients treated with CIC and no patients treated with BDP. No occurrences of visual disturbance were reported in these patients or in the study population as a whole. • There were no clinically meaningful adverse effects of CIC on HPA-axis or on any clinical laboratory analyte or vital sign. • Significant improvements in FEV_1 were seen for both the CIC and BDP treatment groups from baseline to the end of study. The LS mean change in FEV_1 was 0.11 L for both treatment groups (95% CI for CIC 0.04, 0.18 and for BDP 0.02, 0.20). *Conclusion:* In this trial, the overall safety profile of ciclesonide and beclomethasone dipropionate HFA at doses up to 320 mcg twice-daily was comparable. The incidence of oral candidiasis was lower for ciclesonide compared to beclomethasone HFA. There were no meaningful differences between the active groups in HPA-axis function. These findings support the conclusion that ciclesonide at daily doses up to 320 mcg twice-daily are safe and effective for the maintenance treatment of severe persistent asthma as prophylactic therapy.

MC=multicenter, R=randomized, DB=double-blind, LABA=long-acting beta-agonist, MDI=metered-dose inhaler, CIC=ciclesonide, BDP=beclomethasone dipropionate, FEV_1=forced expiratory volume in 1 second, PEF=peak expiratory flow

Table E.6 Evidence Table Spreadsheet for Pivotal Trials for Ciclesonide Once-Daily in the Treatment of Mild-Moderate Persistent Asthma in Adolescents and Adults

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
321	Phase III, MC, R, DB, PCO	• CIC 80 mcg Q_{AM} • CIC 160 mcg Q_{AM} • CIC 320 mcg Q_{AM} • Placebo	526	12 weeks	Inclusion: • ≥12 years of age • Mild-moderate persistent asthma for 6 months prior • Nonsmoker for at least 1 year • FEV_1 of 60% to 85% predicted normal • Reversibility of FEV_1 by 12% or more after 2 inhalations of albuterol	Primary: • AM pre-dose FEV_1 Secondary: • AM PEF • Total asthma symptom score • Albuterol use • AQLQ • Treatment-emergent adverse events	*Results*: • Patient age: Between 12 and 72 years of age with a median age of 36.6 years. • The mean FEV_1 percent predicted at baseline was 70.9%. • CIC 80 mcg (0.12 L, p=0.0123) and 320 mcg (0.15 L, p=0.0014) showed statistically significant improvements from baseline to week 12 in FEV_1 compared to the placebo group but not CIC 160 mcg. • All CIC treatment groups showed significant improvements from baseline in morning PEF ($P \leq 0.0032$) compared to placebo. • All CIC groups demonstrated significant and sustained improvements in total asthma symptom scores compared to the placebo group ($P \leq 0.0146$). • Daily albuterol use was significantly reduced in all CIC treatment groups ($P < 0.0001$). • Statistically significant increases in overall AQLQ scores from baseline to study end were also observed for all 3 CIC treatment groups versus placebo. • Fewer patients discontinued their CIC treatment (3.8% to 7.0%) than those who received placebo (16.4%). • Adverse events reported in more than 7% of patients in any treatment group included: asthma aggravated (CIC 80 4.5%, CIC 160 5.5%, CIC 320 2.3%, Placebo 15.7%), nasopharyngitis (CIC 80 8.3%, CIC 160 7.8%, CIC 320 6.1%, Placebo 4.5%), upper respiratory tract infection (CIC 80 8.3%, CIC 160 6.3%, CIC 320 5.3%, Placebo 7.5%). • Oropharyngeal adverse events were similar between groups: oral candidiasis (CIC 80 1.5%, CIC 160 0%, CIC 320 1.5%, Placebo 0%), pharyngitis (CIC 80 3.8%, CIC 160 4.7%, CIC 320 3.8%, Placebo 4.5%), and hoarseness (CIC 80 0.8%, CIC 160 0%, CIC 320 0.8%, Placebo 0.7%). • There were no significant differences from baseline to Week 12 in peak cortisol concentrations or 24-hour urinary cortisol concentrations for CIC or placebo patients.

QAM=every morning, MC=multicenter, R=randomized, DB=double-blind, PCO=placebo-controlled, FEV=forced expiratory volume, PEF=Peak expiratory flow, AQLQ=Juniper Asthma Quality of Life Questionnaire, PEF peak expiratory flow, CIC=ciclesonide

Table E.7 Evidence Table Spreadsheet for Pivotal Trials for Ciclesonide Once-Daily in the Treatment of Mild-Moderate Persistent Asthma in Adolescents and Adults

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
322	Phase III, MC, R, DB, PCO	• CIC 80 mcg QD_{AM} • CIC 160 mcg QD_{AM} • CIC 320 mcg QD_{AM} • Placebo	489	12 weeks	Inclusion: • ≥12 years of age • Mild-moderate persistent asthma for 6 months prior • Nonsmoker for at least 1 year • FEV_1 of 60% to 85% predicted normal • Reversibility of FEV_1 by 12% or more after 2 inhalations of albuterol	Primary: • AM pre-dose FEV_1 Secondary: • AM PEF • Total asthma symptom score • Albuterol use • AQLQ • Treatment-emergent adverse events	*Results*: • Patient age: Between 11 and 79 years of age with a median age of 36.5 years. • The mean FEV_1 percent predicted at baseline was 71.1%. • All CIC treatment groups showed statistically significant improvements from baseline to week 12 in FEV_1 compared to the placebo group ($p \leq 0.0224$). • CIC 160 mcg and 320 mcg-treated patients showed significant improvements from baseline in morning PEF ($p \leq 0.0171$) compared to placebo • CIC 80 mcg and 160 mcg-treated patients demonstrated significant and sustained improvements in total asthma symptom scores compared to the placebo group ($p \leq 0.0060$). • Daily albuterol use was significantly reduced in all CIC treatment groups ($p<0.0002$). • Statistically significant increases in overall AQLQ scores from baseline to study end were also observed for all 3 ciclesonide treatment groups versus placebo. • Fewer patients discontinued their CIC treatment (3.3% to 4.8%) than those who received placebo (14.4%). • Overall, the frequency of treatment-emergent adverse events was comparable for all treatment groups (CIC 80 mcg QD_{AM}, 62.1%; CIC 160 mcg QD_{AM}, 65.9%; CIC 320 mcg QD_{AM}, 65.3%; and placebo, 66.9%). • Adverse events reported in more than 10% of patients in any treatment group included: nasopharyngitis (CIC 80 9.7%, CIC 160 10.6%, CIC 320 12.9%, Placebo 10.2%), headache (CIC 80 8.1%, CIC 160 13.0%, CIC 320 12.9%, Placebo 11.9%), upper respiratory tract infection (CIC 80 15.3%, CIC 160 7.3%, CIC 320 7.3%, Placebo 12.7%), and asthma aggravated (CIC 80 8.1%, CIC 160 2.4%, CIC 320 2.4%, Placebo 17.8%). • Oropharyngeal adverse events were similar between groups: oral candidiasis (CIC 80 0.8%, CIC 160 0%, CIC 320 1.6%, Placebo 0.8%), pharyngitis (CIC 80 7.3%, CIC 160 3.3%, CIC 320 6.5%, Placebo 5.9%), and hoarseness (CIC 80 0%, CIC 160 0%, CIC 320 0.8%, Placebo 0%). • There were no significant differences from baseline to Week 12 in peak cortisol concentrations or 24-hour urinary cortisol concentrations for CIC or placebo patients.

QAM=every morning, MC=multicenter, R=randomized, DB=double-blind, PCO=placebo-controlled, FEV=forced expiratory volume, PEF=Peak expiratory flow, AQLQ=Juniper Asthma Quality of Life Questionnaire

Table E.8 Evidence Table Spreadsheet for Ciclesonide- Comparison of Twice-Daily Inhaled Ciclesonide and Fluticasone Propionate in Patients with Moderate-to-Severe Persistent Asthma

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
103/2005; Bateman et al, 2008	MC, R, OL, PG	• CIC 320 mcg BID • FP 330 mcg BID	528	6 months	Inclusion: • 12 to 75 years of age • History of bronchial asthma for at least 6 months • Documentation of inhaled corticosteroid at a stable dose for at least 4 weeks prior to screening (FP 500-1000 µg/day or equivalent) • FEV_1 ≥80% at least four hours after rescue and at least 24 hours after controller medication • Reversibility ≥12% after 200-400 µg of salbutamol or a PEF fluctuation ≥15% during at least 3 day of the 7 day run-in period • At least one symptom-free day during 7 day run-in period	Primary: • Change in AM pre-dose FEV_1 from baseline to Week 24 Co-primary: • Drop-out rate due to asthma exacerbation Secondary: • FVC • FEV_1 percent predicted • PEF • Asthma symptom scores • Rescue medication use • AQLQ scores • Treatment-emergent adverse events	*Results*: • Patient age: 12-75, median 43 to 44 years. • FEV_1 percent predicted at baseline was 93.0%. • The increase in AM pre-dose FEV_1 from baseline to Week 24 for CIC was 0.011 L and for FP was 0.024 L. The AM pre-dose FEV_1 change from baseline treatment difference (LS mean) between the CIC and FP treatment groups was non-significant [-0.013 L (-0.070, 0.044), p>0.05] indicating non-inferiority. • Asthma exacerbations that required treatment with an oral corticosteroid occurred in 6 CIC patients and 7 FP patients. • The LS mean change in FVC from baseline to Week 24 between the CIC and FP treatment groups also demonstrated non-inferiority (-0.001 L for CIC and 0.044 L for FP, p>0.05). • Morning, evening and site-measured peak expiratory flow rate improved in both of the treatment groups significantly (change from baseline 8.6 L/min for CIC and 8.4 L/min for FP, both p<0.05). • A reduction from baseline in asthma symptom scores (-0.14 for both CIC and FP, p <0.0001 for CIC and p =0.0001 for FP) and rescue medication use (-0.07 puffs/day for CIC, p =0.0005 and -0.14 puffs/day for FP, p <0.0001) was seen in both treatment groups. • The overall AQLQ score improved significantly from baseline in both treatment groups (0.18 for CIC and 0.15 for FP, both p <0.05). • The frequency of treatment-emergent adverse events was similar between groups (61.2% for CIC and 63.0 for FP). • The most common adverse events that occurred in ≥4% in either treatment group were nasopharyngitis (11.8% for CIC and 8.8% for FP), upper respiratory tract infection (8.2% for CIC and 7.3% for FP), pharyngolaryngeal pain (4.3% and 4.4%), asthma (3.9% for CIC and 5.5% for FP), bronchitis (3.5% for CIC and 4.0% for FP), influenza (3.1% for CIC and 4.4% for FP), headache (2.4% for CIC and 4.4% from FP), dysphonia and oral candidiasis. • Overall, oropharyngeal adverse events were significantly less in the CIC group compared to the FP group (dysphonia: 3.1% vs. 9.2% and oral candidiasis: 2.0% vs. 4.8%; p=0.0023).

OL= open label, R= randomized, MC= multicenter, PG= parallel group, CIC= ciclesonide, FP=fluticasone propionate, AQLQ=Asthma Quality of Life Questionnaire, FEV_1=forced expiratory volume in one second, FVC=forced vital capacity, PEF=peak expiratory flow

Table E.9 Evidence Table Spreadsheet for Ciclesonide- Ciclesonide, a Novel Inhaled Steroid, Does Not Affect Hypothalamic-Pituitary-Adrenal Axis Function in Patients with Moderate-to-Severe Persistent Asthma

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
103; Szefler et al, 2005	R, DB, PG, PC, DD	• CIC 320 mcg or 640 mcg BID • FP 440 mcg or 880 mcg BID • Placebo	59	29 days	Inclusion: • 18 years of age or older • History of moderate to severe persistent asthma for at least 3 months with FEV_1 between 40% and 80% of predicted • Reversibility ≥12% after two inhalations of albuterol • Normal HPA-axis function • Demonstrate proper use of oral inhaler	Primary: • Change from baseline to Day 29 in serum cortisol $AUC_{0\text{-}24hr}$ Secondary: • Serum cortisol after cosyntropin stimulation • 24-hr urinary cortisol • Treatment-emergent adverse events	*Results*: • Patient age: 22-66, median 43 years. • FEV_1 percent predicted at baseline was 56-65%. • Following 29 days of treatment, the primary endpoint, mean change from baseline in 24-hour serum cortisol AUC in mcg*hr/dL was 18.5, -4.1, and 0.7 for CIC 320 mcg BID, CIC 640 mcg BID, and FP 440 mcg BID compared to -19.6 for placebo. This change was not significant for all groups except the high dose FP where there was a statistically significant suppression of serum cortisol $AUC_{0\text{-}24hr}$ from baseline compared to the CIC 800 mcg BID group (p=0.0013) and placebo (p =0.0009). The effects observed with the comparator corticosteroid validate the sensitivity of the study to assess the effect of CIC on the HPA axis. • There were no significant differences among treatment groups in response to cosyntropin stimulation. • There was a significant increase in 24-hour urinary cortisol concentration in the CIC 320 mcg BID group compared to placebo (p =0.0224). There were no statistically significant differences in 24-hour urinary cortisol concentration for the other treatment groups when compared to placebo. • The incidence of treatment-emergent adverse events was similar for all treatment groups compared to placebo (58.3% for both CIC treatment groups, 41.7% for FP 440 mcg BID, 58.3% for FP 880 mcg BID, and 58.3% for the placebo group). • The most common adverse treatment-emergent events that occurred were headache (6 placebo patients, 10 CIC patients and 9 FP patients), sinus headache (0 placebo patients, 1 CIC patient and 2 FP patients), influenza-like illness (2 placebo patients, none from other groups), and sinusitis (3 FP patients, none from other groups).

R= randomized, DB= double blind, PG= parallel group, PC= placebo controlled, DD= double dummy, CIC= ciclesonide, FP=fluticasone propionate, FEV_1=forced expiratory volume in one second

Table E.10 Evidence Table Spreadsheet for Ciclesonide-
Ciclesonide BID vs. Beclomethasone Dipropionate BID, Efficacy and Safety

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
184/2004 Adachi et al, 2007	MC, R, OL, PG	• CIC 400 mcg Q_{PM} (ex-valve, 320 mcg ex-actuator) • CIC 400 mcg BID (ex-valve, 320 mcg ex-actuator) • BDP 400 mcg BID + spacer	319	8 weeks	Inclusion: • 16 to 75 years of age • Moderate to severe asthma • ICS for at least 4 weeks prior to randomization • FEV_1 <80% predicted	Primary: • PEF Secondary: • Spirometric measurements • Use of rescue medication • Change in asthma score	*Results*: • Patients were between 36 and 68 years of age (mean 51.6 to 52.4). • Mean baseline FEV_1 between 67.3% and 70.5%. • Morning PEF increased by 16.02 L/min in the CIC QD_{PM} group, 23.98 L/min in the CIC BID group, and 5.91 L/min in BDP group. Superiority was demonstrated in the CIC BID group compared to the BDP group (p<0.001). Non-inferiority was demonstrated in the CIC QD_{PM} group compared to the BDP group (p <0.001). The change in the morning PEF was greater in the CIC BID group than in the CIC QD_{PM} group, although the difference was not statistically significant (p =0.112). • Evening PEF increased from baseline by 9.17 L/min in the CIC QD_{PM} group, 18.69 L/min in the CIC BID group, and 5.37 L/min in the BDP group. The increase from baseline in evening PEF for the CIC BID group was significantly greater than that for the BDP group (p =0.021). • The use of rescue medication remained at the same level as during the baseline period in the CIC QD_{PM} group (-0.01 puffs/day) and BDP group (+0.07 puffs/day), whereas it decreased in the CIC BID group (-0.44 puffs/day). The difference in the use of rescue medication was significant between the CIC BID group compared to the BDP group (p =0.007) and compared to the CIC QD_{PM} group (p=0.029). • Asthma score decreased over time in both of the CIC treatment groups compared to BDP. The differences in score between the CIC BID group and the BDP group were significant at week 8 (p=0.008). • The frequency of treatment-emergent adverse events that occurred in this trial were comparable between treatment groups (62.3% for CIC QD, 67.3 for CIC BID, 56.6% for BDP). Adverse events occurring in 3% or more of patients in any group included nasopharyngitis (29.2% CIC QD, 37.4% CIC BID, 35.9% BDP), upper respiratory tract inflammation (8.5% CIC QD, 7.5% CIC BID, 6.6% BDP), headache (1.9% CIC QD, 5.6% CIC BID, 1.9% BDP), and pharyngitis (0.9% CIC QD, 3.7% CIC BID, 3.8% BDP). • Oral candidiasis was not reported and mild hoarseness occurred rarely in patients (1 patient in CIC QD_{PM}, 3 patients in CIC BID, and 1 patient in BDP).

R= randomized, MC= multi-center, OL= open label, PG= parallel-group, CIC= ciclesonide, BDP=beclomethasone dipropionate, FEV_1=forced expiratory volume in one second, PEF=peak expiratory flow

Table E.11 Evidence Table Spreadsheet For Clinical Trial 3027-Ciclesonide HFA vs. Beclomethasone HFA for Lens Opacification

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
3027	R, DB,MC, MN, AC	• CIC 320 mcg twice daily • BDP 320 mcg twice daily	1568	12 months	Inclusion • 18 years and older • Moderate to severe persistent asthma for at least 2 months prior to screening • FEV_1 of ≥40% and ≤85% predicted at screening • Use of inhaled corticosteroid therapy at any dose for ≥1 month prior to screening • Non-smoker for at least the past year and <10-pack year history if a previous smoker	Primary: • Occurrence of a Class I lens event for nuclear opalescence, cortical, or posterior subcapsular lens opacification within 12 months Secondary *(Opthalmologic):* • Change from baseline at 12 months in LOCS III grade for (a) nuclear opalescence, (b) cortical opacity, (c) posterior subcapsular opacity • Occurrence of a Class II lens event or cataract surgery within 12 months in either eye	*Results*: • CIC was non-inferior to BDP according to life table estimates for the mITT population (p<0.0001). • CIC met the criteria for non-inferiority versus BDP: Estimated RR ratio of CIC to BDP for Class I lens events was 0.940 and the upper bound of the one-sided 97.5% confidence interval was 1.077 (which was lower than NIB of 1.333). *Secondary:* • Class II, sustained Class II, and Class III lens events were all lower than the prespecified NIBs. • The RR ratios for each of these endpoints were all below 1. • Mean maximum changes (least square means) from baseline in LOCS III grade during the study in either eye were comparable for each type of opacity [see below (a)-(c)]. Mean change from baseline at Month 12 in LOCS III grade was lower than the maximum changes from baseline in LOCS III grade over the course of the study. (a) nuclear opalescence- CIC: 0.22; BDP: 0.23 (b) cortical opacity- CIC: 0.14; BDP: 0.16 (c) posterior subcapsular- CIC: 0.06; BDP: 0.05 *Pulmonary Assessments:* • The increase in FEV_1 between baseline and end of study was 1.14% predicted vs. 1.76% predicted for CIC and BDP, respectively. There was no significant difference between the groups (95% CI: 1.497, 0.249). *Safety Assessments:* • The percentage of subjects with TEAEs was comparable in the CIC and BDP groups (83.5% and 85.6%, respectively). • The most common TEAE in the CIC group was nasopharyngitis (20.9% compared to 17.5% in the BDP group). • Other common TEAEs included sinusitis, asthma, and headache, all of which has a frequency of >10% in both treatment groups.

Table E.11 Evidence Table Spreadsheet For Clinical Trial 3027-Ciclesonide HFA vs. Beclomethasone HFA for Lens Opacification (cont.)

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
						Secondary *(Opthalmologic) (cont.):* • Occurrence of a Class III lens event or cataract surgery within 12 months in either eye • Change from baseline at 12 months in best-corrected visual acuity (BCVA) • Change from baseline at 12 months in intraocular pressure (mm Hg) Secondary *(Other):* • Asthma Control: pulmonary function tests • Safety: Treatment-emergent adverse events (TEAE)	

R= randomized, DB=double-blind, MC= multi-center, MN= multi-national, AC= active-control, mITT= modified intent-to treat population, RR- Relative Risk, NIB- non-inferiority bound, TEAE=treatment-emergent adverse events

Table E.12 Evidence Table Spreadsheet for Ciclesonide- Similar Efficacy of Ciclesonide Once-Daily Versus Fluticasone Propionate Twice-Daily in Patients with Persistent Asthma

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
369/2003; Magnussen et al, 2007	R, DB, DD, PG	• CIC 80 mcg QD_{PM} • CIC 160 mcg QD_{PM} • FP 88 mcg BID	808	12 weeks	Inclusion: • 12 to 75 years of age • Persistent asthma for 6 months • FEV_1 of 61% to 90% predicted normal • Reversibility of FEV_1 by 15% or more after 2 inhalations of albuterol	Primary: • Change in FEV_1 from baseline to the end of treatment • Change in nighttime asthma symptom score from baseline to the end of treatment Secondary: • Morning PEF • Rescue medication use • Days with asthma control • Treatment-emergent adverse events	*Results*: • Patient age: 12-75, mean age of 31 years. • FEV_1 percent predicted at baseline was 78-79%. • After the 12-week treatment period, the CIC 80, CIC 160, and FP groups achieved similar improvements in FEV_1 (0.412 L, 0.378 L, and 0.437 L, respectively; $p<0.0001$ for all). Both doses of CIC were found to be non-inferior to FP 88 mcg BID. • Nighttime asthma symptom score significantly improved from baseline for all treatment groups, as did daytime asthma symptom score (nighttime score: -0.25 for all groups, $p<0.0001$; daytime score: -0.43 for CIC 80, -0.36 for CIC 160, and -0.43 for FP, $p<0.0001$for all groups). • The improvements in morning PEF were significant for all groups ($p<0.0001$) with non-inferiority concluded for the CIC 160 group compared to the FP group. • Evening PEF improved for all treatment groups ($p<0.0001$) and non-inferiority was determined for both CIC groups compared to the FP group. • All 3 treatment groups also significantly reduced rescue medication use versus baseline (-0.58 puffs/day for CIC 80 and -0.57 puffs/day for CIC 160 and FP, $p<0.0001$ versus baseline for all groups), with no statistically significant differences among treatment groups. • The days with asthma control were similar among all treatment groups with no statistically significant differences. • Treatment-emergent adverse events were reported in 25.2%, 24.4%, and 27.4% of patients in the CIC 80 group, CIC 160 mcg group, and FP group, respectively. • Nasopharyngitis (CIC 80 2.2%, CIC 160 3.0%, and FP 5.8%), asthma (CIC 80 2.5%, CIC 160 1.9%, and FP 3.1%), allergic rhinitis (CIC 80 2.2%, CIC 160 1.9%, and FP 2.3%), bronchitis (CIC 80 2.2%, CIC 160 0.4%, and FP 0.8%), pharyngitis (CIC 80 2.5%, CIC 160 1.9%, and FP 1.2%), seasonal allergy (CIC 80 1.8%, CIC 160 3.0%, and FP 1.9%), and allergic rhinitis (CIC 80 2.2%, CIC 160 1.9%, and FP 2.3%) were among the most frequently reported adverse events in ≥2% of patients in any one of the treatment groups. • The incidence of oral candidiasis and oral fungal infection was low (<1%) and similar among groups.

R= randomized, DB= double blind, DD= double dummy, PG= parallel group, CIC= ciclesonide, FP=fluticasone propionate; FEV_1=forced expiratory volume in one second, PEF=peak expiratory flow

Table E.13 Evidence Table Spreadsheet for Comparable Efficacy of Ciclesonide Once-Daily Versus Fluticasone Propionate Twice-Daily in Asthma

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
196/2002; Buhl et al, 2006	MC, R, DB, DD, P	• CIC 160 µg QD_{PM} • FP 88 µg BID	529	12 weeks	Inclusion: • Age ≥12 years • Diagnosis of asthma for 6 months • Maintained on a constant dose of ICS of up to 500 mcg/day beclomethasone or equivalent in the 4 weeks prior to the baseline period • FEV_1 of 80% to 100% predicted	Primary: • FEV_1 Co-primary: • FVC • PEF (AM) Secondary: • PEF (PM) • Asthma symptom scores • Rescue medication use	*Results*: • Patient age: 12-74, median 38-39 years. • FEV_1 percent predicted at baseline was 75% • During the 12-week treatment period, CIC and FP achieved similar improvements in FEV_1. • CIC produced similar improvements from baseline in FEV_1 by the end of treatment (0.489 L and 0.499 L for CIC and FP patients, respectively, $p<0.0001$ for both groups). The LS mean difference in FEV_1 between CIC and FP treatments was -0.010 [95% CI (-0.085,0.066), $p=0.801$] demonstrating non-inferiority of CIC and FP. • The change from baseline to end of treatment in FVC were similar in the CIC and FP groups (3.195 L and 3.322 L, respectively; $p<0.0001$ for both groups). The LS mean difference in FVC between CIC and FP treatments was 0.031 [95% CI (-0.053, 0.115), $p=0.468$]. • The change from baseline in AM PEF was 33 L/min for CIC and 36 L/min for FP with an LS mean difference between treatments of -3 L/min [95% CI (-13, 7), p=0.582]. • At 12 weeks, treatment with CIC and FP both produced significant decreases in the total asthma symptoms scores (-0.75 for CIC and -0.86 for FP, $p<0.0001$ for both groups). There were no significant differences in the change in asthma symptoms scores between treatment groups. • The use of rescue medication from baseline decreased for both groups (-1.00 puffs/day for ciclesonide and -1.21 puffs/day for FP, $p<0.0001$ for both) with no significant between-group differences. • Treatment-emergent adverse events were experienced by 36% of patients in the CIC group and 34% of patients in the FP group. • The most frequently reported adverse events in ≥4% of patients in both treatment groups were upper respiratory tract infection (8% in both groups), bronchitis (4% in CIC and 3% in FP), headache (3% in CIC and 4% in FP), and pharyngitis (4% in CIC and 3% in FP). • Oral candidiasis or voice alteration occurred in 3 patients treated with FP (1%) but in none of the patients receiving CIC.

MC=multicenter, R=randomized, DB=double-blind, DD=double-dummy, P=parallel, ICS=Inhaled Corticosteroids, FEV_1= forced expiratory volume in one second, PEF=Peak Expiratory Flow, FVC= Forced Vital Capacity

Table E.14 Evidence Table Spreadsheet for Adults and Adolescents – QD Dosing Trials (Active-Control; Budesonide)

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
193/2000 Hansel et al, 2006	MC, R	• CIC 80 mcg QD_{AM} • CIC 320 mcg QD_{AM} • BUD 200 mcg BID	554	12 weeks	Inclusion: • Age 12 to 75 years • Mild to moderate asthma for ≥6 months	Primary: • FEV_1 Secondary: • PEF(AM) • Asthma symptoms score • Rescue medication use	*Results*: • Patient age: 12-74, mean 38-45 years. • FEV_1 percent predicted at baseline was 72%. • Significant increases from baseline in FEV_1 were observed in all three treatment groups at 12 weeks of treatment (0.267 L for CIC 80, 0.256 L for CIC 320, and 0.355 L for BUD, all $p<0.001$ for all groups). • Differences between the three treatment groups were not statistically significant, indicating the non-inferiority of CIC to BUD. • Morning PEF was improved significantly at Week 12 from baseline in all three treatment groups (12 L/min, $p=0.008$ for CIC 80, 17 L/min, $p<0.001$ for CIC 320, and 21 L/min, $p<0.001$ for BUD). • Differences in AM PEF between the three treatment groups were not statistically significant, indicating the non-inferiority of CIC to BUD. • Over the 12-week treatment period, significant improvements from baseline were found in median daily asthma symptom scores in all three treatment groups (-0.43 for CIC 80, -0.62 for CIC 320, and -0.57 for BUD, $p<0.001$ for all groups). • There were significant decreases from baseline in the mean number of puffs/day of rescue medication in all treatment groups at week 12 (-0.68, -1.00, and -1.04 with CIC 80, CIC 320, and BUD respectively, all $p<0.001$). • The percentage of patients with treatment-emergent adverse events was similar across all three treatment groups (36.8% for CIC 80, 40.8% for CIC 320, and 33.9% for BUD). • The most frequently reported adverse events in ≥4% of patients were upper respiratory tract infection (11.5% in CIC 80, 5.1% in CIC 320, and 7.9% in BUD), asthma (4.4% in CIC 80, 6.1% in CIC 320, and 4.0% in BUD), bronchitis (3.8% in CIC 80, 6.1% in CIC 320, and 4.0% in BUD) and rhinitis (2.7% in CIC 80, 3.6% in CIC 320, and 4.5% in BUD). • The mean 24-hour, urinary cortisol excretion (nmol/mmol creatinine) at Week 12 was statistically similar to baseline in both CIC treatment groups (-0.54 for CIC 80 and +0.16 for CIC 320), but was significantly reduced from baseline in the BUD treatment group (-1.42, $p<0.05$).

MC=multicenter, R=randomized, CIC=ciclesonide, BUD=budesonide, FEV_1= forced expiratory volume in one second, PEF=Peak Expiratory Flow

Table E.15 Evidence Table Spreadsheet for Comparison of the Efficacy of Ciclesonide 160 g QD and Budesonide 200 g BID in Adults with Persistent Asthma: A Phase III, Randomized, Double-Dummy, Open-Label Study

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
88/2003 Niphadkar et al, 2005	Phase III, R, MC, DB, DD, PG, Open label (BUD)	• CIC 160 mcg QD_{AM} • CIC 160 mcg QD_{PM} • BUD 200 mcg • BID	405	12 weeks	Inclusion: • Age 18 to 69 years • Persistent asthma for ‡6 months maintained on a constant dose of ICS for 4 weeks prior to baseline • FEV_1 of ‡70% predicted • Stable asthma • Good overall health	Primary: • FEV_1 Secondary: • FVC • PEF(AM) • Asthma symptoms • Rescue medication use	*Results:* • The median patient age range was 29 to 32 years of age. • The mean FEV_1 percent predicted at baseline was 93%. • No significant differences were found among the treatment groups with regard to the change in AM pre-dose FEV_1 from baseline to Week 12 [LS mean for CIC vs. BUD was -0.036 L (-0.118, 0.045), p=0.383 for CIC 160 QD_{AM} and 0.022 L (-0.061,0.105), p =0.598 for CIC 160 QD_{PM}]. • FVC and AM PEF were maintained during the 12 week period in all three treatment groups. No significant differences were found among the three treatment groups for the secondary endpoints of FVC [LS mean vs. BUD was 0.005˚L (-0.084, 0.094), p =0.905 for CIC 160 QD_{AM} and 0.002 L (-0.088, 0.092), p =0.968 for CIC 160 QD_{PM}] and AM PEF [LS mean vs. BUD was -4.4 L/min (-16.4, 7.5), p =0.464 for CIC 160 QD_{AM} and 9.3 L/min (-2.8, 21.5), p =0.131 for CIC 160 QD_{PM}]. • All three treatment groups maintained asthma symptom scores during the 12-week treatment period, and no significant differences were found among the treatment groups. • The use of rescue medication was maintained versus baseline, and no significant differences were found between the treatment groups (percentage of days free of rescue medication was 89% for CIC QD_{AM}, 91% for CIC QD_{PM}, and 93% for BUD). • The occurrence of treatment-emergent adverse events was comparable for all treatment groups (17% for CIC˚QD_{AM}, 24% for CIC QD_{PM}, and 21% for BUD). The most commonly reported adverse events in ‡2% of patients in any treatment group were asthma aggravated (9.3% in CIC QD_{AM}, 9.9% for CIC QD_{PM}, and 10.5% for BUD), upper respiratory tract infection NOS (2.1% for CIC˚QD_{AM}, 3.1% for CIC˚QD_{PM}, and 3.8% for BUD), and rhinitis NOS (1.4% for CIC˚QD_{AM}, 0.8% for CIC QD_{PM}, and 3.0% for BUD). • No oropharyngeal adverse events were reported in any of the three treatment groups.

MC=multicenter, R=randomized, DB=double-blind, DD=double-dummy, PG=parallel-group, ICS=Inhaled Corticosteroids, FEV_1= forced expiratory volume in one second, PEF=Peak Expiratory Flow, FVC= Forced Vital Capacity

Table E.16 Evidence Table Spreadsheet For Ciclesonide in the Treatment of Severe Asthma in Adolescents

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
59/2005 Vermeulen et al, 2007	MC, R, DB, DD	• CIC 320 mcg QD_{PM} • BUD 800 mcg QD_{PM}	403	12 weeks	Inclusion: • 12 to 17 years of age • Severe asthma for 6 months • [Run-In]: FEV_1 >50% to <80% predicted • [Run-In]: Not well controlled with budesonide 400 mcg/day for ≥4 weeks prior to study • [Randomization]: >15% reversibility of FEV_1 after salbutamol inhalation	Primary: • Change in PM pre-dose FEV_1 from baseline to Week 12 (or last measurement) Secondary: • Change in AM PEF • Asthma symptom scores • Rescue medication use • Quality of life questionnaire (QOL) • Safety (Treatment Emergent Adverse Events-TEAE)	*Results:* • Patient age: median 14 years. • FEV_1 % predicted at baseline was 73.1% to 73.2%. • At Week 12, significant increases in FEV1 from baseline were observed in both the CIC (0.505 L, p <0.0001 and BUD (0.536 L, p <0.0001) treatment groups. There were no significant differences between groups [-0.031(-0.138, 0.076)]. • AM PEF significantly increased from baseline to Week 12 by 8.0 L/min in the CIC group (p =0.0424). Changes in AM PEF in BUD did not reach statistical significance. • Asthma symptom scores were reduced in both groups: -0.07 for CIC (p <0.0005) and -0.14 for BUD (p <0.0001), with no statistically significant differences between groups. • The median use of rescue medication was reduced to zero puffs per day in the CIC and BUD groups at Week 12. • Overall QOL scores were improved in both groups: 0.19 for CIC (p +0.0001) and 0.18 for BUD (p =0.0056). • Treatment-emergent adverse events occurred in 26.5% of CIC patients and 18.3% of BUD patients. The most commonly reported adverse events in ≥2% of patients in any treatment group included pharyngitis (CIC 5.9%, BUD 3.8%), asthma aggravated (CIC 3.3%, BUD 1.5%), nasopharyngitis (CIC 2.6%, BUD 0.8%) and upper respiratory tract infection (CIC 2.2%, BUD 2.3%). • There were no cases of confirmed candidiasis or events of hoarseness in this trial. • Median 24-hour urine cortisol levels significantly decreased from baseline to Week 12 in the BUD group (15.9-13.7 nmol cortisol/mmol creatinine, p =0.0086). The change in the CIC group was not significant (15.9-16.5 nmol cortisol/mmol creatinine, p =0.1125). The difference between treatment groups was significant (p=0.0012).

MC=multicenter, R=randomized, DB=double-blind, DD=double-dummy, FEV_1= Forced Expiratory Volume in one second, PEF=Peak Expiratory Flow, FVC= Forced Vital Capacity, TEAE=treatment-emergent adverse event

Table E.17 Evidence Table Spreadsheet for Pivotal Trials For Ciclesonide in the Treatment of Mild-Moderate Persistent Asthma in Children

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
341 Gelfand et al, 2006	MC, R, DB, PCO	• CIC 40 mcg QD_{AM} • CIC 80 mcg QD_{AM} • CIC 160 mcg QD_{AM} • Placebo (PBO) QD_{AM}	514	12 weeks	Inclusion: • 4 to 11 years of age • History of asthma for ≥6 months • FEV_1 ≥40% and ≤90% after ≥6 hours without use of a $beta_2$-agonist • Maintained on inhaled coritcosteroids and/or leukotriene receptor antagonists and/or cromones **(Stratum 1)** or bronchodilators only **(Stratum 2)** for 30 days prior to screening • **Stratum 1**: FEV_1 reduction of ≥10% from screening baseline • **Stratum 2**: (must meet ≥1 or more of the following): –Asthma symptom score was ≥3 for at ≥3 of 7 days prior to randomization –Albuterol use was ≥2 puffs/day for ≥3 of 7 days prior to randomization	Primary: • Change in AM pre-dose FEV_1% predicted between baseline and Week 12 Secondary: • Change in FEV_1 and AM PEF from baseline to Week 12 • Total Asthma Severity Rating Score • Rescue medication use • Quality of Life Assessments (PAQLQ) • Safety (Treatment Emergent Adverse Events-TEAE) • Serum cortisol	*Results*: • Patient age: mean was 8.1 years of age. • Mean FEV_1 percent predicted at baseline was 67.9%. • At Week 12, improvements from baseline FEV_1 percent predicted was 13.76% for CIC 40 (p=NS vs. PBO), 16.54% for CIC 80 (p =0.046 vs. PBO), 15.95% for CIC 160 (p =NS vs. PBO) and 12.61% for PBO. • FEV_1 improved from baseline to Week 12 in CIC 80 (+0.32L, p =0.0259 vs. PBO) but not in CIC 40 and 160 groups. • Mean baseline to Week 12 increases in AM PEF were 25.30 L/min (p =0.0003 vs. PBO) in the CIC 80 group and 18.66 L/min (p =0.0343 vs. PBO) in the CIC 160 group. • CIC 80 and CIC 160 demonstrated significant improvements in baseline 24-hour asthma symptoms scores at Week 12 (-1.25 and -1.12, respectively, p <0.05 for both) compared to the PBO group (-0.52). • The mean number of albuterol puffs/day decreased from baseline to Week 12 in the CIC 80 and 160 groups vs. PBO [-0.94 puffs/day (p =0.0002) and -0.88 puffs/day (p =0.0011), respectively; PBO= -0.12 puffs/day]. • The CIC 80 group resulted in significant improvements in overall PAQLQ (+0.77, p =0.0353 vs. PBO). • The incidence of treatment-emergent adverse events was comparable in all four treatment groups (CIC 40: 64.3%, CIC 80: 61.5%, CIC 160: 71.4%, placebo: 67.7%). • The most common treatment-emergent adverse events that occurred in more than 10% of any patient group were asthma aggravated (CIC 40: 14.3%, CIC 80: 15.6%, CIC 160: 16.0%, and placebo: 21.5%), nasopharyngitis (CIC 40: 8.7%, CIC 80: 12.6%, CIC 160: 10.9%, and placebo: 11.5%), sinusitis (CIC 40: 11.1%, CIC 80: 11.9%, CIC 160: 7.6%, and placebo: 7.7%), and headache (CIC 40: 10.3%, CIC 80: 13.3%, CIC 160: 12.6%, and placebo: 13.1%). • There were no reports of hoarseness or oral candidiasis in this trial. Pharyngitis was reported in 6.3% of CIC 40, 8.1% of CIC 80, 6.7% of CIC 160, and 6.9% of placebo patients. • New lenticular opacity was reported in two patients in the placebo group at study endpoint and in one patient in the CIC 160 group 72 days after the last dose. There were no reports of glaucoma in this trial. • Decreases in serum cortisol concentration upon cosyntropin stimulation were seen in all CIC treatment groups, however, the p values were not determined due to small sample size (cortisol measurements were only done in a subset of patients at certain study sites). There was no consistent pattern of changes in 24-hour urinary free cortisol concentrations seen in any of the CIC treatment groups; the p values were not determined due to small sample size.

MC=multicenter, R=randomized, DB=double-blind, PCO=placebo controlled, FEV_1= Forced Expiratory Volume in one second, PEF=Peak Expiratory Flow, CIC=ciclesonide, PBO=placebo, PAQLQ=pediatric asthma quality of life questionnaire, TEAE=treatment-emergent adverse events

Table E.18 Evidence Table Spreadsheet for Pivotal Trials For Ciclesonide in the Treatment of Mild-Moderate Persistent Asthma in Children

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
342 Gelfand et al, 2006	MC, R, DB, PCO	• CIC 40 mcg QD_{AM} • CIC 80 mcg QD_{AM} • CIC 160 mcg QD_{AM} • Placebo QD_{AM}	517	12 weeks	Inclusion: • 4 to 11 years of age • History of asthma for ≥6 months • FEV_1 ≥40% and ≤90% after ≥6 hours without use of a $beta_2$-agonist • Maintained on inhaled coritcosteroids and/or leukotriene receptor antagonists and/or cromones **(Stratum 1)** or bronchodilators only **(Stratum 2)** for 30 days prior to screening • **Stratum 1**: FEV_1 reduction of ≥10% from screening baseline • **Stratum 2**: (must meet ≥1 or more of the following): –Asthma symptom score was ≥3 for at ≥3 of 7 days prior to randomization –Albuterol use was ≥2 puffs/day for ≥3 of 7 days prior to randomization	Primary: • Change in AM pre-dose FEV_1% predicted between baseline and Week 12 Secondary: • Change in FEV_1 and AM PEF from baseline to Week 12 • Total Asthma Severity Rating Score • Rescue medication use • Quality of Life Assessments (PAQLQ) • Safety (Treatment Emergent Adverse Events-TEAE) • Serum cortisol	*Results*: • Mean patient age: 8.3 years. • Mean FEV_1 percent predicted at baseline was 68.8%. • At Week 12, improvements from baseline FEV_1 percent predicted was 9.96% for CIC 40 (p=NS vs. PBO), 10.32% for CIC 80 (p =NS vs. PBO), 12.15% for CIC 160 (p =0.0283 vs. PBO) and 8.61% for PBO. • FEV_1 improved from baseline to Week 12 in CIC 160 (+0.28L, p =0.0118 vs. PBO) but not in CIC 40 and 80 groups. • Only the CIC 40 group demonstrated significant increases from mean baseline AM PEF to Week 12. [+16.45L/min (p =0.0396) vs. PBO (+8.66L/min)]. • All CIC groups demonstrated significant improvements in baseline 24-hour asthma symptom Week 12 (-0.59, -0.50, and -0.51 for CIC 40, CIC 80, and CIC 160 groups, respectively, p <0. groups) compared to PBO (-0.02). • The mean number of albuterol puffs/ day decreased from baseline to Week 12 in all CIC groups but was statistically significant in the CIC 80 group [-0.42 puffs/day (p =0.0288) vs. PBO (-0.03 puffs/day)]. • All CIC groups resulted in significant improvements in overall PAQLQ vs. PBO (CIC 40- 0.42 (p =0.0058), CIC 80- 0.31 (p =0.044), CIC 160- 0.41 (p =0.0048), and PBO- 0.05). • The incidence of treatment-emergent adverse events was comparable in all four treatment groups (CIC 40 59.7%, CIC 80 61.6%, CIC 160 67.2%, placebo 71.7%). • The most common treatment-emergent adverse events that occurred in more than 10% of any patient group were nasopharyngitis (CIC 40 5.4%, CIC 80 13.6%, CIC 160 14.9%, and placebo 8.7%), pharyngitis (CIC 40 10.1%, CIC 80 7.2%, CIC 160 11.2%, and placebo 10.2%), asthma aggravated (CIC 40 9.3%, CIC 80 8.8%, CIC 160 9.7%, and placebo 15.7%), and upper respiratory tract infection (CIC 40 10.1%, CIC 80 10.4%, CIC 160 9.0%, and placebo 13.4%). • Oral candidiasis was reported in 1 (0.8%) CIC 80 patient and 2 (1.5%) CIC 160 patients. Hoarseness was reported in 1 (0.8%) CIC 40 patient with no other reports. Pharyngitis results are listed above. • Lenticular opacity was reported in one patient in the CIC 40 group and one patient in the CIC 80 group. Both of these patients had no lenticular opacity at baseline. There were no reports of glaucoma in this trial. • Changes in serum cortisol concentration upon cosyntropin stimulation and 24-hour urinary free cortisol concentration were seen in all CIC treatment groups, however, the p values were not determined due to small sample size (cortisol measurements were only done in a subset of patients at certain study sites).

MC=multicenter, R=randomized, DB=double-blind, PCO=placebo controlled, FEV_1= Forced Expiratory Volume in one second, PEF=Peak Expiratory Flow, PBO=placebo, CIC=ciclesonide, PAQLQ=pediatric asthma quality of life questionnaire, TEAE=treatment-emergent adverse events

Table E.19 Evidence Table Spreadsheet for Ciclesonide-Long-term Safety Extension of Pediatric Trial

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
341 LT	Phase III, MC (26 US sites), R, OL, safety extension of 341	• CIC 160 mcg QD_{AM} for at least 2 weeks with titration to lowest effective dose (40 mcg or 80 mcg QD_{AM} if possible) • FDP 100 mcg (ex-valve) BID for at least 2 weeks with titration to lowest effective dose (50 mcg BID if possible)	N=193 (CIC: FDP 2:1)	12 months	Inclusion: • 4 to 11 years of age • History of mild, moderate, or severe asthma • Extension of patients in study 341 • Included patients that didn't initially qualify for 341 due to respiratory function parameters	Primary: • Safety Treatment-emergent adverse events, clinical lab values (including serum cortisol and 24-hour urinary cortisol), physical exams, vital signs, local AEs, and eye evaluations	*Results:* • Patient age: 4-12, median 8.4 years. • Mean FEV_1 percent predicted at baseline was 80.9%. • TEAE: CIC 79.8% and FP 81.3%. • AEs (reported by >10% of patients in any treatment group) were asthma NOS (CIC 29.5%, FDP 21.9%), nasopharyngitis (CIC 22.5%, FDP 17.2%), upper respiratory tract infection NOS (CIC 14.7%, FDP 21.9%), viral infection NOS (CIC 7.0%, FDP 10.9%), sinusitis NOS (CIC 15.5%, FDP 14.1%), ear infection NOS (CIC 10.9%, FDP 4.7%), pyrexia (CIC 14.0%, FDP 14.1%) and headache (CIC 14.0%, FDP 9.4%). • Patients who did not complete more than 50 weeks of medication: CIC 29.5% and FDP 31.2%. • The changes from baseline in mean basal serum cortisol concentrations before low-dose cosyntropin stimulation were minimal and non-significant in both treatment groups [CIC 1.4 mcg/dL (95% CI: -1.9, 4.6) and FDP -1.4 (95% CI: -5.4, 2.6)]. Changes from baseline in 24-hour urinary free cortisol concentrations were minimal and non-significant in both treatment groups [CIC 1.95 mcg/day (SD 5.54) and FDP -1.99 mcg/day (SD 3.60)]. • Local TEAEs were reported as follows: oral candidiasis (CIC 0%, FDP 1.6%), pharyngitis (CIC 2.3%, FDP 3.1%), pharyngolaryngeal pain (CIC 5.4%, FDP 7.8%), and hoarseness (0% both groups). • A treatment-emergent lenticular opacity was observed in 3 patients in the CIC group (2.3%). There were no cases of lenticular opacity observed in the FDP group. There were no cases of glaucoma in either treatment group. • In terms of efficacy, asthma control, as measured by FEV_1, improved from baseline to end of study and was maintained throughout the study in both the CIC and the FDP groups.

MC=multicenter, R=randomized, OL=open label, FEV_1= Forced Expiratory Volume in one second, CIC=ciclesonide, FDP=fluticasone dry powder inhaler, TEAE=treatment-emergent adverse events

Table E.20 Evidence Table Spreadsheet for Ciclesonide-Long-term Safety Extension of Pediatric Trial

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
342 LT	Phase III, MC (26 US sites), R, OL, safety extension of 342	• CIC 160 mcg QD_{AM} for at least 2 weeks with titration to lowest effective dose (40 mcg or 80 mcg QD_{AM} if possible) • FDP 100 mcg (ex-valve) BID for at least 2 weeks with titration to lowest effective dose (50 mcg BID if possible)	N=190 (CIC: FDP 2:1)	12 months	Inclusion: • 4 to 11 years of age • History of mild, moderate, or severe asthma • Extension of patients in study 341 • Included patients that didn't initially qualify for 341 due to respiratory function parameters	Primary: • Safety Treatment-emergent adverse events, clinical lab values (including serum cortisol and 24-hour urinary cortisol), physical exams, vital signs, oropharyngeal exams, and eye exams	*Results:* • Patient age: 4-12, median 8.6 years. • Mean FEV_1 percent predicted at baseline was 79.5%. • TEAE: CIC 85.9% and FP 73.8%. • AEs (reported by >10% of patients in any treatment group) were asthma NOS (CIC 32.8%, FDP 16.4%), nasopharyngitis (CIC 25.0%, FDP 16.4%), upper respiratory tract infection NOS (CIC 26.6%, FDP 16.4%), sinusitis NOS (CIC 10.2%, FDP 18.0%), otitis media NOS (CIC 10.2%, FDP 3.3%), pyrexia (CIC 15.6%, FDP 11.5%) and headache (CIC 14.1%, FDP 14.8%). • There was a greater percentage of patients who permanently discontinued the trial in the CIC group (CIC 8.6% and FDP 1.6%). • Patients who did not complete more than 50 weeks of medication: CIC 27.3% and FDP 30.6%. • Very few patients had data available for serum or urinary free cortisol analyses. Of the data that was collected, there were no meaningful difference between baseline and end of study basal or 24-hour urinary free cortisol concentration.' • Local TEAEs were reported as follows: oral candidiasis (CIC 1.6%, FDP 3.3%), pharyngitis (CIC 0.8%, FDP 0.0%), pharyngolaryngeal pain (CIC 9.4%, FDP 8.2%), and hoarseness (0% both groups). • There were no patients in the CIC group and one patient in the FDP group who had treatment-emergent lenticular opacity at the follow-up exam. One CIC patient was diagnosed with low-tension glaucoma during the treatment period. • In terms of efficacy, asthma control as measured by FEV_1, improved from baseline to end of study and was maintained throughout the study in both the CIC and FDP groups.

MC=multicenter, R=randomized, OL=open label, FEV_1= Forced Expiratory Volume in one second, CIC=ciclesonide, FDP=fluticasone dry powder inhaler, TEAE=treatment-emergent adverse events

Table E.21 Evidence Table Spreadsheet for the Assessment of Ciclesonide on Growth in Children with Asthma

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
343; Skoner et al 2008	MC, R, DB, PCO, non-inferiority	• CIC 40 mcg QD_{AM} • CIC 160 mcg QD_{AM} • Placebo	661	52 weeks	Inclusion: • 5 to 8.5 years of age • History of mild persistent asthma for at least 3 months prior to Visit 1 • FEV_1 of ≥80% of predicted following at least a 4-hour albuterol withhold • Treated with non-corticosteroid asthma medications on an as-needed or daily basis, or with low doses of ICS for at least one month prior to Visit 1 • Patients were to be classified in Stage 1 or less in the Tanner classification of sexual maturity	Primary: • Velocity of growth during the double-blind treatment period Secondary: • Bone age was determined using wrist radiographs • Treatment-emergent adverse events • Urine samples were also collected to assess cortisol measurements	*Results*: • Patient age: Between 5 and 8.6 years of age with a mean age of 6.7 years. • The mean FEV_1 percent predicted range was 96% to 96.2% • The mean range in stadiometric height at randomization was 122.6 cm to 123.4 cm. • Wrist x-ray assessments at randomization identified 48.1% and 33.3% of all patients with high bone age and normal bone age, respectively. • Mean growth velocity at the run-in period was slightly lower in the CIC 160 mcg treatment group (6.20 cm/year) compared with the other groups (6.59 cm/year and 6.49 cm/year for CIC 40 mcg and placebo, respectively). Overall growth rates were lower during the double-blind treatment period compared with the run-in and follow-up periods. • Mean differences from placebo (5.75 cm/year) in growth velocity over the double-blind treatment period were -0.02 cm/year for CIC 40 mcg and -0.15 cm/year for CIC 160 mcg (p=0.0001 for both CIC groups vs placebo indicating non-inferiority). • The shift in chronologic age relative to bone age range from baseline to the end of the study was comparable among the treatment groups. A high ratio of chronological age to bone age is indicative of growth retardation. • There were only 17 subjects with shifts from a normal or low ratio to a high ratio between the run-in and double-blind treatment periods with higher frequencies of these shifts occurring in the placebo (7 patients, 4.0%) or CIC 40 mcg (8 patients, 4.3% groups than in the CIC 160 mcg group (2 subjects, 1.1%). • Treatment-emergent adverse events occurred in 94.6%, 90.0% and 89.6% of patients in the CIC 80 mcg, CIC 160 mcg, and placebo groups, respectively. • The most common treatment-emergent adverse event in ≥10% of patients in any group (CIC 40 mcg, CIC 160 mcg, and placebo) were asthma (33.5%, 29.7%, and 33.9%), nasopharyngitis (31.7%, 31.1%, and 26.2%), pyrexia (28.1%, 20.1%, and 19.9%), headache (18.6%, 19.6%, and 18.1%), upper respiratory infection (14.0%, 12.8%, and 11.8%), influenza (13.1%, 10.0%, and 9.0%), bronchitis (10.4%, 10.0%, and 10.0%), rhinitis (10.0%, 5.9%, and 9.5%), and pharyngitis.

Table E.21 Evidence Table Spreadsheet for the Assessment of Ciclesonide on Growth in Children with Asthma (cont.)

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
							Results: • The incidence of local oropharyngeal adverse events were comparable in the CIC 40 mcg, CIC 160 mcg, and placebo groups: oral candidiasis, 0%, 0%, and 0.5%; pharyngolaryngeal pain, 3.6%, 4.1%, and 3.6%; pharyngitis, 16.3%, 12.8%, and 15.4%; and hoarseness, 0% in all groups. • The change from baseline to the end of the double-blind treatment period in 24-hour urinary free cortisol (corrected for creatinine) was -0.002 mcg/mg, -0.003 mcg/mg, and -0.002 mcg/mg for the CIC 40 mcg, CIC 160 mcg and placebo groups, respectively (p=NS for either CIC group versus placebo). *Conclusion*: Conclusions cannot be drawn from this trial since compliance could not be confirmed (not sure if patients took their ciclesonide inhaler as directed), blood levels were not measured and no difference in efficacy measures between the placebo and ciclesonide treatment groups were seen.

MC=multicenter, R=randomized, DB=double-blind, PCO=placebo-controlled, AM=morning, QD=once daily, ICS=inhaled corticosteroid, FEV_1= Forced Expiratory Volume in one second, CIC=ciclesonide

Table E.22 Evidence Table Spreadsheet For Ciclesonide in Children and Adolescents with Persistent Asthma

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
54/2003 Pedersen et al, 2006	MC, R, DB, PG,	• CIC 80 mcg BID • FP 88 mcg BID	556	12 weeks	Inclusion: • Between 6 and 15 years of age • Diagnosis of persistent asthma for 6 months • Clinically stable for 4 weeks • FEV_1 between 50% and 90% predicted normal	Primary: • FEV_1 Secondary: • PEF • Rescue medication use • Asthma symptom score • Safety	*Results*: • Patient age range: 6 to 16 years of age, mean age 10 years. • Mean FEV_1 percent predicted at baseline was 80%. • FEV_1 improved by 0.285 L for patients in the CIC and FP treatment groups ($p<0.0001$ for both groups vs. baseline). • Statistically significant increases ($p<0.0001$ for both treatment groups) in morning PEF (30.8 L/min for CIC, 33.7 L/min for FP) were observed in both treatment groups. Comparable results were demonstrated for evening PEF ($p<0.0001$ vs. baseline for both treatment groups). • Median total asthma symptom scores improved from 1.43 to 0.00 in the CIC group and 1.29 to 0.00 in the FP treatment groups ($p<0.0001$ for both groups). • Changes in asthma symptom scores and rescue medication use were not statistically significant between CIC and FP treatment groups. • A similar percentage of treatment-emergent adverse events occurred in both treatment groups (CIC 35.7% and FP 33.0%). The most commonly reported adverse events occurring in 3% or more of the patients in either treatment group were rhinitis (CIC 7.9%, FP 8.2%), upper respiratory tract infection (CIC 6.9%, FP 6.5%), pharyngitis (CIC 4.3%, FP 3.9%), asthma (CIC 3.6%, FP 2.9%), headache (CIC 3.6%, FP 2.5%), and sinusitis (CIC 1.8%, FP 3.2%). • The incidence of oropharyngeal adverse events such as sore throat (CIC 1.4%, FP 0.7%), pharyngitis (CIC 4.3%, FP 3.9%), voice alteration (CIC 0%, FP 0.4%), and oral candidiasis (CIC 0%, FP 0.7%) was low and similar in both treatment groups. • The 24-hour free urine cortisol adjusted for creatinine increased from baseline to treatment endpoint in both treatment groups with a significant increase occurring only in the CIC group (LS mean difference +2.361 nmol/mmol creatinine, p=0.040). The difference between the treatment groups was not statistically significant.

MC=multi-center, R=randomized, DB=double-blind, PG=parallel-group, PEF=Peak Expiratory Flow, BID=twice daily, FEV_1= Forced Expiratory Volume in one second, CIC=ciclesonide, FP=fluticasone propionate

Table E.23 Evidence Table Spreadsheet for Comparison of the Efficacy and Safety of Ciclesonide 160 mcg Once-Daily versus Budesonide 400 mcg Once-Daily in Children with Asthma

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
278/2004 Von Berg et al, 2007	MC, R, DB, DD, PG	• CIC 160 µg Q_{PM} • BUD 400 µg Q_{PM}	621	12 weeks	Inclusion: • Ages 6 to 11 years • Persistent asthma for ≥6 months	Primary: • FEV_1 Secondary: • PEF(AM) • Asthma symptom scores • Rescue medication use • PAQLQS and PACQLQ scores Safety: • Body height • 24-hour urinary cortisol	*Results:* • The mean age of patients in this trial was 9 years of age (range 6-11 years of age). • The mean FEV_1 percent predicted at baseline was between 77% and 78%. • Treatment with CIC and BUD achieved statistically significant increases in FEV_1 after 12 weeks of treatment (0.220 L and 0.253 L per protocol analysis (PP), p <0.0001 for both treatment groups vs. baseline; 0.232 L and 0.250 L intent-to-treat analysis (ITT), p<0.0001 for both treatment groups vs. baseline). Non-inferiority of CIC versus BUD was demonstrated for FEV_1 (p=0.0009 for CIC non-inferiority PP; p <0.0001 for CIC non-inferiority ITT). • Treatment with CIC and BUD achieved statistically significant increases in morning PEF after 12 weeks of treatment (22.5 L/min and 26.3 L/min, p <0.0001 vs. baseline, PP; 22.7 L/min and 25.0 L/min, p <0.0001 vs baseline, ITT). • Both the CIC and BUD groups achieved statistically significant improvements in asthma symptom score sum after 12 weeks of treatment (-1.21 for both, PP; -1.18 and -1.19, respectively, ITT, p<0.0001 versus baseline for both groups, both analyses). • Both the CIC and BUD groups achieved a statistically significant reduction in the need for rescue medication after 12 weeks of treatment (-1.64 puffs/day for both, PP; -1.58 and -1.64 puffs/day ITT, respectively, p<0.0001 vs. baseline for both groups, both analyses). • The difference between treatment groups for changes in asthma symptom scores and rescue medication use was not statistically significant. • Both treatment groups achieved statistically significant improvements in overall scores versus baseline on the PAQLQ(S) and PACQLQ (CIC 0.73 and 0.92, BUD 0.74 and 0.98, PP; CIC 0.69 and 0.88, BUD 0.70 and 0.96, ITT; all p<0.0001 for both analyses). Non-inferiority of CIC versus BUD was demonstrated in the PAQLQ(S) and PACQLQ (ITT, p<0.5738).

Table E.23 Evidence Table Spreadsheet for Comparison of the Efficacy and Safety of Ciclesonide 160 mcg Once-Daily versus Budesonide 400 mcg Once-Daily in Children with Asthma (cont.)

Ref.	Design	Treatment	N	Time	Demographics	End Points	Results/Comments
							Results: • Treatment-emergent adverse events occurred in approximately 38% of patients in both treatment groups. • The following treatment-emergent adverse events occurred in 3% or more of patients in either group: asthma aggravated (CIC 4.1%, BUD 1.0%), pharyngitis (CIC 6.0%, BUD 6.8%), nasopharyngitis (CIC 4.1%, BUD 5.4%), and upper respiratory tract infection (CIC 3.6%, BUD 6.3%). • The frequency of patients reporting oropharyngeal adverse events, including oral candidiasis and dysphonia, was low in both groups (CIC 0.2%, BUD 1.5%). • Body height increased by 1.18 cm and 0.70 cm in the CIC and BUD groups, respectively, after 12 weeks of treatment (both $p<0.0001$ versus baseline). The increase in body height was significantly greater in CIC patients than in BUD patients ($p=0.0025$). • After 12 weeks, treatment with CIC and BUD resulted in statistically significant decreases (-2.17 [-6.9%] and -5.16 [-22.9%] nmol/mmol creatinine) in 24-hour urinary cortisol adjusted for creatinine (both $p<0.0001$ versus baseline). The decrease in 24-hour urinary cortisol was significantly greater in the BUD group compared with the CIC group ($p<0.0001$).

MC=multicenter, R=randomized, DB=double-blind, DD=double-dummy, PG=parallel-group, FEV_1= Forced Expiratory Volume in one second, PEF=Peak Expiratory Flow, PAQLQS= Pediatric Asthma Quality of Life Questionnaire, PACQLQ= Pediatric Asthma Caregiver's Quality of Life Questionnaire

2.3 Outcomes Studies and Economic Evaluation Supporting Data

Prospective, Trial-based Cost-effectiveness Studies

At the time that this dossier went to press, no prospective, cost-effectiveness trials evaluating ALVESCO in patients with asthma have been completed. Additional research opportunities evaluating ALVESCO, including economic analyses and updated economic modeling using the U.S. approved BID dosing, are currently being pursued.

Retrospective Cost-Effectiveness Studies

Please note that the approved U.S. dosing for ALVESCO Inhalation Aerosol is based on a twice-daily dosing regimen. The approved U.S. dosing for FLOVENT® Inhalation Aerosol (fluticasone propionate) is based on a twice-daily dosing regimen. Fluticasone propionate is approved in other countries with twice-daily dosing and ciclesonide is approved in other countries with once-daily dosing. The following modeling study was done prior to U.S. approval of ALVESCO Inhalation Aerosol.

A modeling study was performed to assess the cost-effectiveness of ciclesonide compared to fluticasone propionate in adult patients with mild to severe asthma. A decision tree model was utilized to simulate the health consequences and costs associated with the twice-daily use of fluticasone propionate or once-daily and twice-daily ciclesonide. The decision tree was based on the probability of the occurrence of adverse drug events, calculated based on the incidence of adverse events experienced in clinical trials with ciclesonide and fluticasone propionate (Study Reports 196/2002, 119/2002, 138/2001, 273/2000, 242/2002, and 81/2001), that may lead to medical care including sore throat, oral candidiasis, dysphonia, and cough. The model parameters that were utilized for the economic analysis included the costs for drug acquisition (parity was assumed), rescue medication usage, and the use of medical resources due to an adverse drug event or a non-symptom-free day.[Taylor]

Results

Overall, the use of ciclesonide was determined to be associated with lower costs ($2.01 vs. $2.02) and more adverse-drug-event-free and symptom-free days (0.254 vs. 0.247) than fluticasone propionate. Using a one-way sensitivity analysis, the model was determined to be most sensitive to changes in symptom-free days and medication cost per day. Cost-effectiveness was demonstrated in this modeling study due to the greater number of symptom-free and adverse-event-free days in ciclesonide treated patients, assuming that drug acquisition costs for fluticasone propionate and ciclesonide are equal.[Taylor]

Cross-sectional or Retrospective Costing Studies and Treatment Pattern Studies

At the time that this dossier went to press, no cross-sectional or retrospective costing studies evaluating treatment patterns have been completed.

Systematic Review Articles

Two systematic Cochrane review articles have been compiled regarding the use of ciclesonide in patients with asthma.

The first Cochrane review article describes eighteen trials (reporting 20 study comparisons) which met the review entry criteria of randomized, parallel or crossover studies where ciclesonide was compared to placebo or where different doses of ciclesonide were compared. Authors report findings from 18 group comparisons where data were available (6343 participants, of whom 1692 were children).

The authors determined that due to the short duration of the included ciclesonide versus placebo studies, there was insufficient data to assess the impact of ciclesonide on asthma exacerbations. At doses of 100 mcg/d or less up to 400 mcg/d (ex-valve) in mild to moderate asthma, the authors found that ciclesonide improved lung function, asthma symptoms and rescue inhaler use, compared with placebo.

When the authors compared the studies on different doses of ciclesonide, 100 mcg/d versus 200 mcg/d, 100 mcg/d versus 400 mcg/d, and 400 mcg/d versus 800 mcg/d (ex-valve), they determined that the results did not yield significant differences in lung function outcomes. The authors decided that the available adverse event data presented in these studies was not sufficient enough in detail to permit assessment of the safety profile of this drug for this review. For trials included in this review, refer to **Appendix 1** at the end of this section.[Manning (CIC vs. placebo)]

The second Cochrane review article describes twenty-one trials involving 7243 participants. These trials were randomized, parallel or crossover studies comparing ciclesonide with other steroids, both at nominally equivalent doses or lower doses of ciclesonide. The authors found that equal daily doses of ciclesonide, beclomethasone (BDP), or budesonide (BUD) gave similar results for peak expiratory flow rates (PEF), although forced vital capacity (FVC) was higher with ciclesonide. The authors' assessment stated that data on forced expired volume in one second (FEV_1) were inconsistent but that withdrawal data and symptoms were similar between treatments. When lower doses of ciclesonide were compared to BDP or BUD, the authors found the difference in FEV_1 did not reach significance but they could not exclude a significant effect in favor of BDP/BUD. The assessment also stated that other lung function outcomes did not give significant differences between treatments of ciclesonide, BDP, or BUD, that pediatric quality of life scores did not differ between treatments, and that adverse events occurred with similar frequency between ciclesonide and BDP/BUD.

The assessment of results from studies in which ciclesonide was compared with the same dose of fluticasone (FP) demonstrated that lung function parameters (FEV_1, FVC, and PEF) did not differ significantly, that pediatric quality of life scores favored ciclesonide, and that the incidence of oral candidiasis was less frequent with ciclesonide, although the authors determined that the other side-effect outcomes did not give significant differences in favor of either treatment. When the authors compared three studies of ciclesonide with FP at half the nominal dose, they determined that FEV_1 was not significantly different, but was not equivalent between the treatments (per protocol: -0.05 L 95% confidence intervals -0.11 to 0.01).[Manning (CIC vs. competitor)]

Quality of Life Studies

Quality of life parameters were measured in three of the efficacy trials submitted for U.S. FDA approval of ALVESCO (Clinical Study Reports 321, 322, and 323/324). In addition, quality of life was a secondary endpoint measured in two once-daily ciclesonide trials completed in pediatric patients.

In the two once-daily ciclesonide trials (Clinical Study Reports 321 and 322) submitted for U.S. FDA approval of ALVESCO, the individual trial results and a combined analysis of quality of life results from both trials were performed using the Juniper Asthma Quality of Life Questionnaire (AQLQ). These were Phase III, 12-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled trials performed in a total of 1015 patients with mild to moderate asthma. Patients were 12 years or older with an FEV_1 percent predicted between 60% and 85%. Patients were randomized to receive ciclesonide 80 mcg QD, 160 mcg QD, 320 mcg QD (ex-actuator), or placebo in the morning. The overall AQLQ score and individual domain scores (activity limitation, symptoms, emotional function, and exposure to environmental stimuli) were measured at baseline, Week 4, and Week 12. Changes in quality of life using the Juniper AQLQ are determined to be clinically important if the difference in the AQLQ overall score reaches the MID (minimally important difference) of 0.5 or greater.[Pearlman, Nathan]

Results

A statistically significant improvement in overall AQLQ score was seen for all treatment groups compared to placebo from baseline to Week 12 in both trials (see **Tables 2.3.1 and 2.3.2**). In Study Report 321, statistically significant improvements were seen for two of the four individual domain scores in all CIC treatment groups (symptoms and emotional function). Significant improvements were not seen in the exposure to environmental stimuli domain changes in the CIC 80 and CIC 160 groups and the activity limitation domain change in the CIC 80 group. In Study Report 322, statistically significant improvements were seen for three of the four individual domain scores in all CIC treatment groups (activity limitation, symptoms, emotional function). Significant improvements were not seen in the exposure to environmental stimuli domain changes for all CIC groups.[DOF 321, 322, Nathan]

Pooled data for Study Reports 321 and 322 indicate that a greater proportion of patients in the CIC treatment groups compared to placebo had an overall AQLQ increase that reached the MID of 0.5 from baseline to Week 12 (CIC 80: 47.1%, CIC 160: 50.0%, CIC 320: 50.6%, placebo: 31.0%).[Nathan]

Table 2.3.1: AQLQ Changes from Baseline to Week 12 from Study Report 321[DOF 321]

				Least-squares mean (SE)		
Variable	Treatment	N	Baseline Mean[a]	Change from baseline	Treatment differences vs. placebo	P-value[b]
Overall Score						
	Placebo	125	4.77	0.15 (0.085)	-	-
	Ciclesonide-80	130	4.44	0.46 (0.083)	0.31 (0.117)	0.0078
	Ciclesonide-160	124	4.84	0.59 (0.086)	0.44 (0.117)	0.0002
	Ciclesonide-320	128	4.65	0.81 (0.084)	0.66 (0.116)	0.0001
Domain 1 - Symptoms						
	Placebo	126	4.56	0.08 (0.093)	-	-
	Ciclesonide-80	130	4.35	0.55 (0.092)	0.46 (0.128)	0.0003
	Ciclesonide-160	124	4.66	0.68 (0.094)	0.60 (0.130)	0.0001
	Ciclesonide-320	128	4.50	0.87 (0.092)	0.79 (0.128)	0.0001
Domain 2 - Activity Limitation						
	Placebo	124	5.10	0.22 (0.088)	-	-
	Ciclesonide-80	127	4.71	0.41 (0.086)	0.19 (0.121)	0.1225
	Ciclesonide-160	121	5.07	0.49 (0.089)	0.27 (0.121)	0.0264
	Ciclesonide-320	124	4.93	0.74 (0.087)	0.51 (0.120)	0.0001
Domain 3 - Emotional Function						
	Placebo	126	4.64	0.06 (0.103)	-	-
	Ciclesonide-80	130	4.22	0.41 (0.102)	0.35 (0.142)	0.0146
	Ciclesonide-160	124	4.75	0.66 (0.104)	0.61 (0.143)	0.0001
	Ciclesonide-320	128	4.59	0.80 (0.102)	0.75 (0.141)	0.0001
Domain 4 - Exposure to Environmental Stimuli						
	Placebo	126	4.68	0.29 (0.093)	-	-
	Ciclesonide-80	130	4.29	0.48 (0.092)	0.19 (0.128)	0.1381
	Ciclesonide-160	124	4.76	0.50 (0.094)	0.21 (0.129)	0.1080
	Ciclesonide-320	128	4.39	0.74 (0.092)	0.45 (0.128)	0.0005

[a] Baseline means are raw means.
[b] P-values are for treatment comparisons versus placebo.
SE = standard error, - = not applicable.

Table 2.3.2: AQLQ Changes from Baseline to Week 12 from Study Report 322 [DOF 322]

Variable	Treatment	N	Baseline Mean[a]	Least-squares mean (SE) Change from baseline	Least-squares mean (SE) Treatment differences vs. placebo	P-value[b]
Overall Score						
	Placebo	108	4.77	0.14 (0.089)	–	–
	Ciclesonide-80	119	4.66	0.54 (0.085)	0.40 (0.122)	0.0010
	Ciclesonide-160	119	4.61	0.63 (0.086)	0.50 (0.121)	0.0001
	Ciclesonide-320	120	4.71	0.57 (0.084)	0.43 (0.121)	0.0004
Domain 1 - Symptoms						
	Placebo	108	4.62	0.11 (0.100)	–	–
	Ciclesonide-80	119	4.49	0.61 (0.096)	0.50 (0.138)	0.0003
	Ciclesonide-160	119	4.45	0.74 (0.097)	0.63 (0.137)	0.0001
	Ciclesonide-320	119	4.58	0.65 (0.095)	0.54 (0.137)	0.0001
Domain 2 - Activity Limitation						
	Placebo	108	5.07	0.17 (0.089)	–	–
	Ciclesonide-80	117	4.97	0.55 (0.086)	0.38 (0.122)	0.0021
	Ciclesonide-160	119	4.91	0.58 (0.086)	0.41 (0.121)	0.0008
	Ciclesonide-320	117	5.04	0.48 (0.085)	0.31 (0.122)	0.0109
Domain 3 - Emotional Function						
	Placebo	110	4.72	-0.01 (0.105)	–	–
	Ciclesonide-80	121	4.49	0.55 (0.100)	0.56 (0.144)	0.0001
	Ciclesonide-160	120	4.40	0.60 (0.102)	0.61 (0.144)	0.0001
	Ciclesonide-320	120	4.50	0.58 (0.100)	0.59 (0.144)	0.0001
Domain 4 - Exposure to Environmental Stimuli						
	Placebo	110	4.48	0.32 (0.095)	–	–
	Ciclesonide-80	121	4.59	0.39 (0.092)	0.07 (0.131)	0.5794
	Ciclesonide-160	120	4.50	0.53 (0.093)	0.21 (0.131)	0.1037
	Ciclesonide-320	120	4.45	0.51 (0.092)	0.19 (0.131)	0.1387

[a]Baseline means are raw means.
[b]P-values are for treatment comparisons versus placebo.
SE - standard error, - not applicable.

Quality of life can be significantly influenced by side-effects that occur while taking medication. The following information summarizes the pooled adverse event data for Study 321 and 322. For adverse event information from the individual trials, please refer to the summary of Study Report 321 and 322 in Section 2.2 of this dossier, Key Clinical and Economic Studies.

The adverse event profile was similar between the treatment groups (CIC 57.6%-59.5%, placebo 59.9%). The frequency of local adverse events were also similar between groups (oral candidiasis: CIC 0%-1.6%, placebo 0.4%; pharyngitis: CIC 4.0%-5.4%, placebo 5.2%; cough: CIC 0.8%-1.6%, placebo 2.0%; hoarseness: CIC 0%-0.8%, placebo 0.4%). More patients discontinued treatment due to asthma-aggravated adverse events in the placebo group (14.3%) compared to the CIC groups (2.7%-3.9%).[Pearlman]

Improvements in quality of life were measured in a Phase III, 12-week, multicenter, double-blind, parallel-group, placebo-controlled trial (Clinical Study Report 323/324) in which 531 patients with severe asthma received ciclesonide or fluticasone propionate. Patients were 12 years of age or older and were required to have an FEV_1 percent predicted between 40% and 65%. Patients received CIC 160 mcg BID, CIC 320 mcg BID, FP 440 mcg BID (ex-actuator doses), or placebo. The overall AQLQ score and individual domain scores (activity limitation, symptoms, emotional function, and exposure to environmental stimuli) were measured at baseline, Week 4, and Week 12. Changes in quality of life using the Juniper AQLQ are determined to be clinically important if the difference in the AQLQ overall score reaches the MID (minimally important difference) of 0.5 or greater.[DOF 323/324]

Results

Improvements in overall AQLQ from baseline to Week 12 were statistically significant in all treatment groups compared to placebo (CIC 160 BID: 0.61, CIC 320 BID: 0.65, FP 440 BID: 0.91, $p<0.0001$, see **Table 2.3.3**). All individual domain scores improved significantly for both CIC groups and the FP group compared to placebo ($p<0.05$). A greater proportion of patients in the CIC and FP treatment groups compared to placebo had an overall AQLQ increase that reached the MID of 0.5 from baseline to Week 12 (CIC 160 BID: 42.5%, CIC 320 BID: 43.1%, FP 440 BID: 58.8%, placebo: 26.9%).[Bernstein, DOF 323/324]

Refer to **Table 2.3.4** for the most frequently reported treatment-emergent adverse events in this trial occurring in 10% or more of any group.

Table 2.3.3: AQLQ Changes from Baseline to Week 12 from Study Report 323/324[DOF 323/324]

Variable	Treatment	N	Baseline Mean[a]	Least-squares mean (SE) Change from baseline	Least-squares mean (SE) Treatment differences vs. placebo	P-value[b]
Overall Score						
	Placebo	129	4.42	-0.11 (0.091)	–	–
	Ciclesonide-320	122	4.46	0.50 (0.093)	0.61 (0.128)	0.0001
	Ciclesonide-640	125	4.35	0.54 (0.091)	0.65 (0.126)	0.0001
	Ciclesonide-880	133	4.54	0.80 (0.089)	0.91 (0.125)	0.0001
Symptoms						
	Placebo	131	4.42	-0.19 (0.102)	–	–
	Ciclesonide-320	122	4.35	0.54 (0.105)	0.74 (0.145)	0.0001
	Ciclesonide-640	126	4.32	0.55 (0.103)	0.75 (0.142)	0.0001
	Ciclesonide-880	132	4.48	0.86 (0.101)	1.06 (0.141)	0.0001
Activity Limitation						
	Placebo	122	4.70	-0.03 (0.093)	–	–
	Ciclesonide-320	121	4.70	0.47 (0.091)	0.50 (0.128)	0.0001
	Ciclesonide-640	120	4.55	0.57 (0.092)	0.60 (0.128)	0.0001
	Ciclesonide-880	129	4.84	0.75 (0.089)	0.79 (0.126)	0.0001
Emotional Function						
	Placebo	132	4.10	-0.11 (0.114)	–	–
	Ciclesonide-320	123	4.35	0.51 (0.117)	0.63 (0.161)	0.0001
	Ciclesonide-640	127	4.06	0.51 (0.115)	0.62 (0.159)	0.0001
	Ciclesonide-880	133	4.17	0.82 (0.113)	0.93 (0.157)	0.0001
Exposure to Environmental Stimuli						
	Placebo	132	4.25	0.08 (0.095)	–	–
	Ciclesonide-320	123	4.32	0.47 (0.097)	0.38 (0.134)	0.0043
	Ciclesonide-640	127	4.15	0.50 (0.095)	0.41 (0.132)	0.0018
	Ciclesonide-880	133	4.38	0.78 (0.094)	0.70 (0.131)	0.0001

[a]Baseline means are raw means.
[b]P-values are for treatment comparisons versus placebo.
SE - standard error, - not applicable.

Table 2.3.4: Treatment-emergent Adverse Events Occuring in ≥10% of Patients in Any Group from Clinical Study Report 323/324

	CIC 160 mcg BID	CIC 320 mcg BID	FP 440 mcg BID	Placebo
Total AEs	**61.4%**	**54.6%**	**60.1%**	**61.8%**
Asthma Aggravated	7.9%	10.8%	2.2%	19.9%
Nasopharyngitis	10.2%	6.9%	10.9%	7.4%
Oral Candidiasis	1.6%	0%	11.6%	2.2%
Pharyngitis	4.7%	3.1%	5.1%	2.9%
Dysphonia	0%	1.5%	3.6%	0.7%

The two pediatric trials that evaluated quality of life endpoints in patients taking once-daily ciclesonide are summarized below. **Please note that ALVESCO Inhalation Aerosol is approved for twice-daily administration in patients 12 years of age and older and is NOT indicated in children under 12 years of age.**

Improvements in quality of life were measured in two identical Phase III, 12-week, randomized, multicenter, double-blind, parallel-group, placebo-controlled trials (Study Reports 341 and 342, Gelfand et al.) in which 1031 children with asthma were randomized to ciclesonide or placebo. Patients were 4 to 11 years of age and were required to have an FEV_1 percent predicted between 40% and 90%. Patients received CIC 40 mcg QD_{AM}, CIC 80 mcg QD_{AM}, CIC 160 mcg QD_{AM} (ex-actuator doses), or placebo. The overall PAQLQ score and individual domain scores (activity limitation, symptoms, and emotional function) were measured at baseline, Week 4, and Week 12. Changes in quality of life using the Juniper AQLQ are determined to be clinically important if the difference in the PAQLQ overall score reaches the MID (minimally important difference) of 0.5 or greater.[Gelfand]

Results

The pooled data from Study Reports 341 and 342 demonstrated that improvements in overall PAQLQ from baseline to Week 12 were statistically significant in all treatment groups compared to placebo (CIC 40 mcg QD_{AM} 0.25, p=0.01; CIC 80 mcg QD_{AM} 0.27, p=0.004; CIC 160 mcg QD_{AM} 0.29, p=0.002). One of the three individual domain scores improved significantly for all CIC groups compared to placebo (symptoms). Significant improvements were not demonstrated in activity limitation for the CIC 40 group and changes in emotional function in the CIC 80 group. A greater proportion of patients in the CIC treatment groups compared to placebo had an overall PAQLQ increase that reached the MID of 0.5 from baseline to Week 12 (CIC 40: 46.1%, CIC 80: 50.0%, CIC 160: 52.5%, placebo: 36.5%, p=0.02).[Miller]

For quality of life results from the individual trials, refer to **Table 2.3.5** and **Table 2.3.6** below. For the most frequently reported treatment-emergent adverse events (≥10% of patients in any group) in the individual trials, refer to **Table 2.3.7** and **Table 2.3.8**.

Table 2.3.5: Quality of Life Changes from Baseline to Week 12 from Study Reports 341[DOF 341]

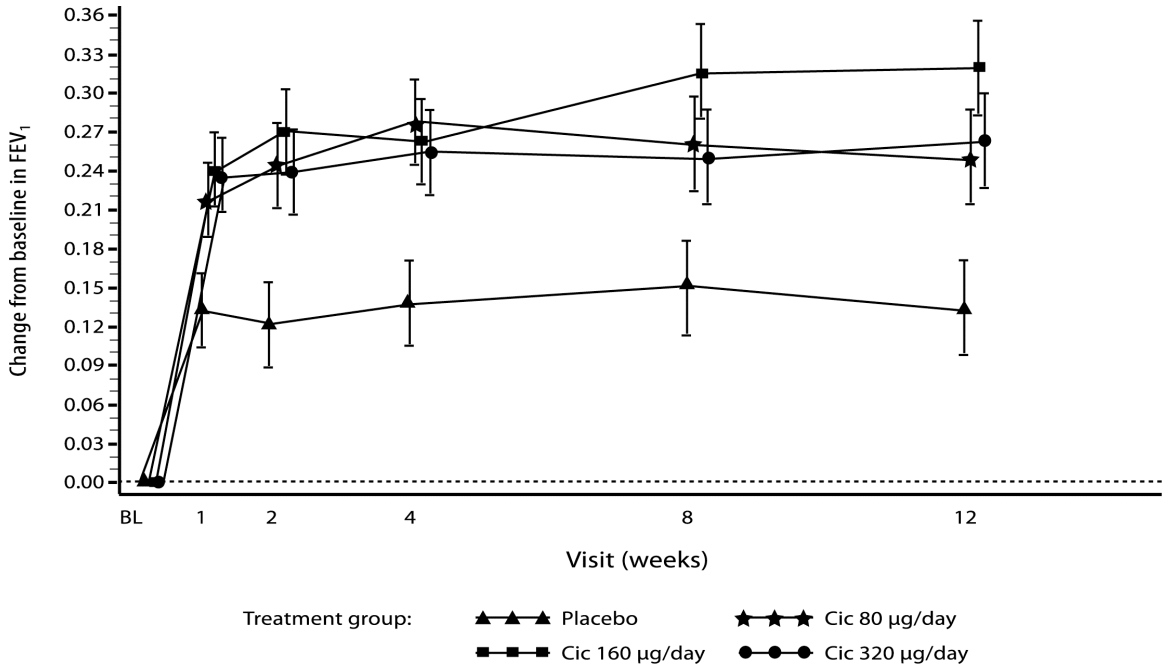


Table 2.3.6: Quality of Life Changes from Baseline to Week 12 from Study Reports 342[DOF 342]

Variable	Treatment	N	Baseline Mean[a]	Least-squares mean (SE) Change from baseline	Least-squares mean (SE) Treatment differences vs. placebo	P-value[b]
Overall Score						
	Placebo	95	5.62	0.05 (0.100)	–	–
	Ciclesonide-40	98	5.38	0.42 (0.100)	0.37 (0.133)	0.0058
	Ciclesonide-80	100	5.59	0.31 (0.099)	0.27 (0.132)	0.0440
	Ciclesonide-160	113	5.47	0.41 (0.093)	0.36 (0.128)	0.0048
Domain 1 - Symptoms						
	Placebo	95	5.46	-0.01 (0.115)	–	–
	Ciclesonide-40	98	5.21	0.48 (0.115)	0.49 (0.154)	0.0016
	Ciclesonide-80	100	5.42	0.36 (0.114)	0.37 (0.152)	0.0153
	Ciclesonide-160	113	5.25	0.45 (0.107)	0.45 (0.148)	0.0023
Domain 2 - Activity Limitation						
	Placebo	95	5.54	0.11 (0.102)	–	–
	Ciclesonide-40	98	5.36	0.34 (0.102)	0.23 (0.136)	0.0933
	Ciclesonide-80	100	5.52	0.38 (0.101)	0.27 (0.135)	0.0458
	Ciclesonide-160	113	5.43	0.46 (0.095)	0.35 (0.131)	0.0075
Domain 3 - Emotional Function						
	Placebo	95	5.88	0.08 (0.105)	–	–
	Ciclesonide-40	98	5.60	0.35 (0.105)	0.28 (0.141)	0.0508
	Ciclesonide-80	100	5.84	0.20 (0.104)	0.13 (0.139)	0.3697
	Ciclesonide-160	113	5.78	0.31 (0.098)	0.24 (0.135)	0.0789

[a]Baseline means are raw means.
[b]P-values are for treatment comparisons versus placebo.
SE - standard error, - not applicable.

Safety Results Study Report 341

Table 2.3.7: Treatment-emergent Adverse Events Occuring in ≥10% of Patients in Any Group from Clinical Study Report 341

	CIC 40 mcg QD	CIC 80 mcg QD	CIC 160 mcg QD	Placebo
Total AEs	**64.3%**	**61.5%**	**71.4%**	**67.7%**
Asthma Aggravated	14.3%	15.6%	16.0%	21.5%
Nasopharyngitis	8.7%	12.6%	10.9%	11.5%
Sinusitis	11.1%	11.9%	7.6%	7.7%
Headache	10.3%	13.3%	12.6%	13.1%

There were no reports of hoarseness or oral candidiasis in this trial. Pharyngitis was reported in 6.3% of CIC 40, 8.1% of CIC 80, 6.7% of CIC 160, and 6.9% of placebo patients.

New lenticular opacity was reported in two patients in the placebo group at study endpoint and in one patient in the CIC 160 group 72 days after the last dose. There were no reports of glaucoma in this trial.

Decreases from baseline in serum cortisol concentration upon cosyntropin stimulation were seen in all CIC treatment groups, however, the p values were not determined due to small sample size (cortisol measurements were only done in a subset of patients at certain study sites). There was no consistent pattern of changes in 24-hour urinary free cortisol concentrations were seen in any of the CIC treatment groups; the p values were not determined due to small sample size.[DOF 341]

Safety Results Study Report 342

Table 2.3.8: Treatment-emergent Adverse Events Occuring in ≥10% of Patients in Any Group from Clinical Study Report 342

	CIC 40 mcg QD	CIC 80 mcg QD	CIC 160 mcg QD	Placebo
Total AEs	**59.7%**	**61.6%**	**67.2%**	**71.7%**
Nasopharyngitis	5.4%	13.6%	14.9%	8.7%
Pharyngitis	10.1%	7.2%	11.2%	10.2%
Asthma Aggravated	9.3%	8.8%	9.7%	15.7%
Upper Respiratory Tract Infection	10.1%	10.4%	9.0%	13.4%

Oral candidiasis was reported in 1 (0.8%) CIC 80 patient and 2 (1.5%) CIC 160 patients. Hoarseness was reported in 1 (0.8%) CIC 40 patient with no other reports. Pharyngitis results are listed above.

Lenticular opacity was reported in one patient in the CIC 40 group and one patient in the CIC 80 group. Both of these patients had no lenticular opacity at baseline. There were no reports of glaucoma in this trial.

Changes from baseline in serum cortisol concentration upon cosyntropin stimulation and 24-hour urinary free cortisol concentration were seen in all CIC treatment groups, however, the *p* values were not determined due to small sample size (cortisol measurements were only done in a subset of patients at certain study sites).[DOF 342]

Improvements in quality of life were measured in a Phase III, 12-week, randomized, double-blind, double-dummy trial (Clinical Study Report 278/2004, von Berg et al.) in which children with asthma received ciclesonide or budesonide. Patients were 6 to 11 years of age and were required to have an FEV_1 of 50% to 90% of predicted in patients receiving rescue medication only, 50% to 100% of predicted in patients pretreated with a constant dose of controller medication other than steroids for at least 30 days before inclusion, or 80% to 105% of predicted in patients pretreated with $\leq$400 mcg/day beclomethasone or equivalent for at least 30 days before inclusion.. Eligible patients were randomized in a 2:1 ratio to receive HFA MDI formulations of ciclesonide 160 mcg (ex-actuator) once-daily in the evening (CIC QD_{PM}, n = 416) or budesonide 400 mcg (ex-valve) once daily administered in the evening (BUD QD_{PM} n = 205) for 12 weeks.[von Berg] The overall PAQLQ (Pediatric Asthma Quality of Life Questionnaire) score, individual domains (symptoms, emotions, activities), and PACQLQ (Pediatric Asthma Caregiver's Quality of Life Questionnaire) score were measured at baseline and Week 12.[DOF 204] Changes in quality of life using the Juniper AQLQ are determined to be clinically important if the difference in the PAQLQ overall score reaches the MID (minimally important difference) of 0.5 or greater.

Results

Improvements in overall PAQLQ from baseline to Week 12 were statistically significant in both treatment groups (CIC- 0.73, $p<0.0001$; BUD- 0.74, $p<0.0001$, see **Table 2.3.9**). All individual domain scores improved significantly for both treatment groups. Improvements in overall PACQLQ from baseline to Week 12 were statistically significant in both treatment groups (CIC- 0.92, $p<0.0001$; BUD- 0.98, $p<0.0001$, see **Table 2.3.10**). A similar proportion of patients in the CIC and BUD treatment groups had an overall increase in PAQLQ and PACQLQ that reached the MID of 0.5 from baseline to Week 12 (CIC- 58.2% and 63.3%, BUD- 53.8% and 60.8%, per population analysis). The corresponding values in the intention to treat population confirmed the conclusions from the per population analyses.[DOF 204, Vermeulen abstract]

Table 2.3.9: PAQLQ Changes from Baseline to Week 12 from Study Report M1-204[DOF 204]

		T0			$T_{end/last}$	$T_{end/last}$ – T0		
		n	Mean	LSMean	LSMean	LSMean ± SEM	95%CI	p-value two-sided
Overall score								
PP	CIC 160 µg od	316	5.55	5.58	6.31	0.73 ± 0.04	0.66, 0.80	< 0.0001
	BUD 400 µg od	160	5.65	5.58	6.32	0.74 ± 0.05	0.64, 0.84	< 0.0001
ITT	CIC 160 µg od	389	5.60	5.61	6.30	0.69 ±0.03	0.63, 0.76	< 0.0001
	BUD 400 µg od	189	5.63	5.61	6.31	0.70 ± 0.05	0.61, 0.80	< 0.0001
Activities								
PP	CIC 160 µg od	316	5.61	5.65	6.30	0.65 ± 0.04	0.57, 0.73	< 0.0001
	BUD 400 µg od	160	5.73	5.65	6.28	0.63 ± 0.06	0.52, 0.74	< 0.0001
ITT	CIC 160 µg od	389	5.63	5.65	6.30	0.65 ± 0.04	0.58, 0.73	< 0.0001
	BUD 400 µg od	189	5.69	5.65	6.28	0.63 ± 0.05	0.53, 0.73	< 0.0001
Emotions								
PP	CIC 160 µg od	316	5.74	5.78	6.40	0.62 ± 0.04	0.54, 0.70	< 0.0001
	BUD 400 µg od	160	5.87	5.78	6.38	0.60 ± 0.06	0.49, 0.71	< 0.0001
ITT	CIC 160 µg od	389	5.80	5.83	6.40	0.57 ± 0.04	0.50, 0.65	< 0.0001
	BUD 400 µg od	189	5.88	5.83	6.38	0.55 ± 0.05	0.44, 0.65	< 0.0001
Symptoms								
PP	CIC 160 µg od	316	5.37	5.39	6.24	0.85 ± 0.04	0.77, 0.94	< 0.0001
	BUD 400 µg od	160	5.42	5.39	6.29	0.90 ± 0.06	0.79, 1 01	< 0.0001
ITT	CIC 160 µg od	389	5.41	5.41	6.22	0.81 ± 0.04	0.73, 0.88	< 0.0001
	BUD 400 µg od	189	5.40	5.41	6.27	0.86 ± 0.05	0.76, 0.97	< 0.0001

Scores range from 1 (maximal impairment) to 7 (no impairment).
BUD = budesonide, CI = confidence interval, CIC = ciclesonide, LSMean = least squares mean (ANCOVA), n = number of patients with data available at T0 and $T_{end/last}$, od = once daily, SEM = standard error of the mean, T0 = randomization visit, T_{end} = last visit (PP endpoint analysis), T_{last} = last visit (ITT endpoint analysis).

Table 2.3.10: PACQLQ Changes from Baseline to Week 12 from Study Report M1-204[DOF 204]

		T0			$T_{end/last}$	$T_{end/last}$ – T0		
		n	Mean	LSMean	LSMean	LSMean ± SEM	95%CI	p-value two-sided
Overall score								
PP	CIC 160 µg od	229	4.81	4.91	5.82	0.92 ± 0.09	0.74, 1.09	< 0.0001
	BUD 400 µg od	120	5.08	4.91	5.89	0.98 ± 0.11	0.76, 1.21	< 0.0001
ITT	CIC 160 µg od	299	4.94	4.98	5.87	0.88 ± 0.08	0.73, 1.03	< 0.0001
	BUD 400 µg od	153	5.06	4.98	5.94	0.96 ± 0.10	0.77, 1.15	< 0.0001
Activities								
PP	CIC 160 µg od	229	5.09	5.18	6.05	0.87 ± 0.10	0.68, 1.06	< 0.0001
	BUD 400 µg od	120	5.34	5.18	6.17	0.99 ± 0.12	0.75, 1.24	< 0.0001
ITT	CIC 160 µg od	299	5.21	5.25	6.09	0.84 ± 0.08	0.68, 1.00	< 0.0001
	BUD 400 µg od	153	5.33	5.25	6.25	1.00 ± 0.10	0.79, 1.20	< 0.0001
Emotions								
PP	CIC 160 µg od	229	4.69	4.78	5.72	0.94 ± 0.09	0.76, 1.12	< 0.0001
	BUD 400 µg od	120	4.97	4.78	5.77	0.99 ± 0.12	0.76, 1.22	< 0.0001
ITT	CIC 160 µg od	299	4.82	4.86	5.77	0.90 ± 0.08	0.75, 1.06	< 0.0001
	BUD 400 µg od	153	4.94	4.86	5.80	0.94 ± 0.10	0.75, 1.14	< 0.0001

Scores range from 1 (maximal impairment) to 7 (no impairment).
BUD = budesonide, CI = confidence interval, CIC = ciclesonide, LSMean = least squares mean (ANCOVA), n = number of patients with data available at T0 and $T_{end/last}$, od = once daily, SEM = standard error of the mean, T0 = randomization visit, T_{end} = last visit (PP endpoint analysis), T_{last} = last visit (ITT endpoint analysis).

Treatment-emergent adverse events occurred in approximately 38% of patients in both treatment groups. The following treatment-emergent adverse events occurred in 3% or more of patients in either group: asthma aggravated (CIC 4.1%, BUD 1.0%), pharyngitis (CIC 6.0%, BUD 6.8%), nasopharyngitis (CIC 4.1%, BUD 5.4%), and upper respiratory tract infection (CIC 3.6%, BUD 6.3%).

The frequency of patients reporting oropharyngeal adverse events, including oral candidiasis and dysphonia, was low in both groups (CIC 0.2%, BUD 1.5%).

Body height increased by 1.18 cm and 0.70 cm in the CIC and BUD groups, respectively, after 12 weeks of treatment (both $p<0.0001$ versus baseline). The increase in body height was significantly greater in CIC patients than in BUD patients ($p=0.0025$).

After 12 weeks, treatment with CIC and BUD resulted in statistically significant decreases (-2.17 [-6.9%] and -5.16 [-22.9%] nmol/mmol creatinine) in 24-hour urinary cortisol adjusted for creatinine (both $p<0.0001$ versus baseline). The decrease in 24-hour urinary cortisol was significantly greater in the BUD group compared with the CIC group ($p<0.0001$).[DOF 204, von Berg]

Compliance Results from ALVESCO Inhalation Aerosol Pivotal Trials

Compliance is an important aspect of patient care and can have significant effects on patient outcomes. The following table (**Table 2.3.11**) summarizes the compliance as measured in the ALVESCO Inhalation Aerosol pivotal trials submitted to the U.S. FDA. Compliance was calculated from the patients' daily diary recordings. Please note that compliance as measured in a clinical trial is considered to be biased as compared to compliance as measured in a real-life setting (i.e. measuring insurance claims over a period of time). At the time of publication of this dossier, no retrospective claims evaluations to evaluate compliance have been completed with ALVESCO Inhalation Aerosol.

Table 2.3.11: Compliance Rates in ALVESCO Inhalation Aerosol Pivotal Trials

Study Report	Poor Compliance with Treatment *Number of patients (%)
321	CIC 80 mcg QD_{AM}- 0 (0%) CIC 160 mcg QD_{AM}- 0 (0%) CIC 320 mcg QD_{AM}- 0 (0%) Placebo- 0 (0%)
322	CIC 80 mcg QD_{AM}- 2 (1.6%) CIC 160 mcg QD_{AM}- 0 (0%) CIC 320 mcg QD_{AM}- 0 (0%) Placebo- 0 (0%)
323/324	CIC 160 BID- 0 (0%) CIC 320 BID- 0 (0%) FP 440 BID- 0 (0%) Placebo- 1 (0.7%)
3030	CIC 160 mcg QD_{AM}- 1 (0.7%) CIC 80 mcg BID- 0 (0%) Placebo- 2 (1.4%)
3031	CIC 160 mcg QD_{AM}- 0 (0%) CIC 80 mcg BID- 2 (1.2%) CIC 80 mcg BID to CIC 160 mcg QD_{AM}- 2 (1.2%) Placebo- 3 (1.7%)
325	CIC 320 BID- 0 (0%) CIC 640 BID- 0 (0%) Placebo- 0 (0%)

* Poor compliance with treatment was defined as having less than 70% of days compliant with expected dose actuations.

Appendix 1: Studies Included in the Cochrane Review of CIC vs. Placebo

Reference	Treatment Arms	Duration	Population
Adachi M, Ishihara K, Inoue H, et al. Efficacy and safety of once-daily inhaled ciclesonide in adults with mild to moderate asthma: A double-blind, placebo-controlled study. *Respirology*. 2007;12:566-572.	-CIC 100 mcg QD (ex-valve, 80 mcg ex-actuator) -CIC 200 mcg QD (ex-valve, 160 mcg ex-actuator) -CIC 400 mcg QD (ex-valve, 320 mcg ex-actuator) -PLB	8 weeks	N=311 16-75 years of age
Adachi M, Ishihara K, Inoue H, et al. Efficacy and safety of inhaled ciclesonide compared with chlorofluorocarbon beclomethasone dipropionate in adults with moderate to severe persistent asthma. *Respirology*. 2007;12:573-580.	-CIC 200 mcg BID (ex-valve, 160 mcg ex-actuator) -CIC 400 mcg BID (ex-valve, 320 mcg ex-actuator) -BDP 400 mcg BID (ex-valve, 320 mcg ex-actuator)	8 weeks	N=316 16-75 years of age
Baena Cagnani 2006 Unpublished data only	-CIC 50 mcg QD (ex-valve, 40 mcg ex-actuator) -CIC 100 mcg QD (ex-valve, 80 mcg ex-actuator) -PLB	12 months	N=661 Median age: 5-8.5 years of age

Appendix 1: Studies Included in the Cochrane Review of CIC vs. Placebo (continued)

Reference	Treatment Arms	Duration	Population
Bateman, E, Karpel J, Casale T, Wenzel S, and Banerji D. Ciclesonide reduces the need for oral steroid use in adult patients with severe, persistent asthma. *Chest*. 2006;129:1176-1187.	-CIC 320 mcg BID -CIC 640 mcg BID -PLB	12 weeks	N=141 12-75 years of age
Bateman ED, Cheung D, Lapa e Silva J, Gohring UM, Schafer M, Engelstatter R. Randomized comparison of ciclesonide 160 and 640 µg/day in severe asthma. *Pulm Pharmacol Ther*. 2008;21:489-498.	-CIC 160 mcg QD_{AM} and placebo QD_{PM} -CIC 320 mcg BID	12 weeks	N=680 12-75 years of age
Bernstein 2004 Unpublished data only	-CIC 200 mcg BID (ex-valve, 160 mcg ex-actuator) -CIC 400 mcg BID (ex-valve, 320 mcg ex-actuator) -FP 1000 mcg BID (ex-valve, 880 mcg ex-actuator) -PLB	12 weeks	N=531 12 years of age and older
Chapman KR, Patel P, D'Urzo AD, et al. Maintenance of asthma control by once-daily inhaled ciclesonide in adults with persistent asthma. Allergy. 2005;60:330-337.	-CIC 160 mcg QD_{AM} -CIC 640 mcg QD_{AM} -PLB	12 weeks	N=329 18-69 years of age

Appendix 1: Studies Included in the Cochrane Review of CIC vs. Placebo (continued)

Reference	Treatment Arms	Duration	Population
DF16153 Unpublished data only	-CIC 100 mcg BID DPI -CIC 200 mcg BID DPI -CIC 400 mcg BID DPI -CIC 400 mcg BID MDI (ex-valve) -CIC 800 mcg BID -PLB	6 weeks	N=1145 >12 years of age
EFC6163a and b Unpublished data only	-CIC 100 mcg BID (ex-valve, 80 mcg ex-actuator) -CIC 200 mcg QD (ex-valve, 160 mcg ex-actuator) -PLB	6 weeks	N=456 Not clear
Gelfand W, Georgitis JW, Noonan M, Ruff ME. Once-daily ciclesonide in children: efficacy and safety in asthma. *J Pediatr*. 2006;148:377-383. (341 and 342)	-CIC 40 mcg QD_{AM} -CIC 80 mcg QD_{AM} -CIC 160 mcg QD_{AM} -PLB	12 weeks	N=1031 (341 and 342) 4 -11 years of age
Hansel TT, Benezet O, Kafé H, et al. A multinational, 12-week, randomized study comparing the efficacy and tolerability of ciclesonide and budesonide in patients with asthma. *Clin Ther*. 2006;28:906-920.	-CIC 80 mcg QD_{AM} -CIC 320 mcg QD_{AM} -BUD 200 mcg BID DPI	12 weeks	N=554 12-75 years of age

Appendix 1: Studies Included in the Cochrane Review of CIC vs. Placebo (continued)

Reference	Treatment Arms	Duration	Population
Langdon CG, Adler M, Mehra S, Alexander M, Drollmann A. Once-daily ciclesonide 80 or 320 µg for 12 weeks is safe and effective in patients with persistent asthma. *Respir Med*. 2005;99:1275-1285.	-CIC 80 mcg QD_{AM} -CIC 320 mcg QD_{AM} -PLB	12 weeks	N=360 18-70 years of age
Lipworth BJ, Kaliner MA, LaForce CF, et al. Effect of ciclesonide and fluticasone on hypothalamic-pituitary-adrenal axis function in adults with mild-to-moderate persistent asthma. *Ann Allergy Asthma Immunol*. 2005;94:465-472.	-CIC 320 mcg QD_{PM} -CIC 320 mcg BID -FP 440 mcg BID -PLB	12 weeks	N=164 18 years of age and older
Magnussen H, Hofman J, Staneta P, Lawo J-P, Hellwig M, Engelstatter R. Similar efficacy of ciclesonide once daily versus fluticasone propionate twice daily in patients with persistent asthma. *J Asthma*. 2007;44:555-563.	-CIC 80 mcg QD_{PM} -CIC 160 mcg QD_{PM} -FP 88 mcg BID	12 weeks	N=808 12-75 years of age and older
O'Connor BJ, Sips P, Biberger C, Steinijans VW, Wurst W. Management of moderate to severe bronchial asthma by ciclesonide: a 12-week study [abstract]. *Allergy*. 2002;57:S73.	-CIC 400 mcg BID (ex-valve, 320 mcg ex-actuator) -CIC 800 mcg BID (ex-valve, 640 mcg ex-actuator)	12 weeks	N=365 Not reported
Pearlman DS, Berger WE, Kerwin E, LaForce C, Kundu S, Banerji D. Once-daily ciclesonide improves lung function and is well tolerated by patients with mild-to-moderate persistent asthma. *J Allergy Clin Immunol*. 2005;116:1206-1212. 321 and 322	-CIC 80 mcg QD_{AM} -CIC 160 mcg QD_{AM} -CIC 320 mcg QD_{AM} -PLB	12 weeks	N=1015 12 years of age and older

Appendix 1: Studies Included in the Cochrane Review of CIC vs. Placebo (continued)

Reference	Treatment Arms	Duration	Population
Wilson AM, Duong M, Pratt B, Dolovich M, O'Byrne PM. Anti-inflammatory effects of once daily low dose inhaled ciclesonide in mild to moderate asthmatic patients. *Allergy*. 2006;61:537-542.	-CIC 160 mcg QD_{AM} -PLB	Cross-over, each arm 4 weeks	N=20 18-71 years of age
Zietkowski Z, Bodzenta-Lukaszyk A, Tomasiak MM, Szymanski W, Skiepko R. Effect of ciclesonide and fluticasone on exhaled nitric oxide in patients with mild allergic asthma. *Respir Med*. 2006;100:1651-1656.	-CIC 80 mcg QD_{PM} -CIC 160 mcg QD_{PM} -FP 100 mcg BID (ex-valve)	12 weeks	N=35 Adults

DB denotes double-blind, PG- parallel-group, OL- open label, CIC- ciclesonide, BDP- beclomethasone dipropionate, PLB- placebo, BUD- budesonide, FP- fluticasone propionate

Appendix 2: Studies Included in the Cochrane Review of CIC vs. Competitor ICS

Reference	Treatment Arms	Duration	Population
Adachi M, Ishihara K, Inoue H, et al. Efficacy and safety of once-daily inhaled ciclesonide in adults with mild to moderate asthma: A double-blind, placebo-controlled study. *Respirology*. 2007;12:566-572.	-CIC 100 mcg QD (ex-valve, 80 mcg ex-actuator) -CIC 200 mcg QD (ex-valve, 160 mcg ex-actuator) -CIC 400 mcg QD (ex-valve, 320 mcg ex-actuator) -PLB	8 weeks	N=311 16-75 years of age
Adler M, Langan J, martinot JB, Croonenborghs L, Gruss C, Oedekoven C. Ciclesonide 160 mcg once daily compared with fluticasone propionate 250 mcg twice daily in maintenance therapy of patients with stable asthma. *Eur Resp J.* 2006;28(Suppl 50):205s.	-CIC 200 mcg QD -FP 250 mcg BID (ex-valve, 220 mcg ex-actuator)	12 weeks	N=111 17-75 years of age
Bateman E, Linnhof AE, Homik L, Freudensprung U, Smau L, Engelstatter R. Comparison of twice-daily inhaled ciclesonide and fluticasone propionate in patients with moderate-to-severe persistent asthma. *Pulm Pharmacol Ther*. 2008;21:264-275.	-CIC 320 mcg BID -FP 330 mcg BID	6 months	N=528 12-75 years of age
Bernstein 2004 Unpublished data only	-CIC 200 mcg BID (ex-valve, 160 mcg ex-actuator) -CIC 400 mcg BID (ex-valve, 320 mcg ex-actuator) -FP 1000 mcg BID (ex-valve, 880 mcg ex-actuator) -PLB	12 weeks	N=531 12 years of age and older

Appendix 2: Studies Included in the Cochrane Review of CIC vs. Competitor ICS (continued)

Reference	Treatment Arms	Duration	Population
Boulet LP, Drollmann A, Magyar P, et al. Comparative efficacy of once-daily ciclesonide and budesonide in the treatment of persistent asthma. *Respir Med*. 2006;100:785-794.	-CIC 320 mcg QD_{AM} -BUD 320 mcg QD_{AM}	12 weeks	N=359 12-75 years of age
Boulet LP, Bateman ED, Voves R, Muller T, Wolf S, Engelstatter R. A randomized study comparing ciclesonide and fluticasone propionate in patients with moderate persistent asthma. *Respir Med*. 2007;101:1677-1686.	-CIC 320 mcg QD_{PM} -FP 200 mcg BID DPI	12 weeks	N=474 12-75 years of age
Buhl R, Vinkler I, Magyar P, et al. Comparable efficacy of ciclesonide once daily versus fluticasone propionate twice daily in asthma. *Pulm Pharmacol Ther*. 2006;19:404-412.	-CIC 160 mcg QD_{PM} -FP 88 mcg BID	12 weeks	N=529 12-75 years of age
BY9010/M1-136 Unpublished data only	-CIC 200 mcg QD (ex-valve, 160 mcg ex-actuator) -BUD 400 mcg QD	12 weeks	N=249 18-75 years of age
BY9010/M1-137 Unpublished data only	-CIC 200 mcg QD (ex-valve, 160 mcg ex-actuator) -BUD 400 mcg QD	12 weeks	N=125 18-75 years of age
BY9010/M1-142 Unpublished data only	-CIC 100 mcg QD (ex-valve, 80 mcg ex-actuator) -FP 100 mcg BID (ex-valve, 88 mcg ex-actuator)	24 weeks	N=480 12-75 years of age

Appendix 2: Studies Included in the Cochrane Review of CIC vs. Competitor ICS (continued)

Reference	Treatment Arms	Duration	Population
Hansel TT, Benezet O, Kafé H, et al. A multinational, 12-week, randomized study comparing the efficacy and tolerability of ciclesonide and budesonide in patients with asthma. *Clin Ther*. 2006;28:906-920.	-CIC 80 mcg QD_{AM} -CIC 320 mcg QD_{AM} -BUD 200 mcg BID DPI	12 weeks	N=554 12-75 years of age
Lee DKC, Haggart K, Currie GP, Bates CE, Lipworth BJ. Effects of hydrofluoroalkane formulations of ciclesonide 400 µg once daily vs fluticasone 250 µg twice daily on methacholine hyper-responsiveness in mild-to-moderate persistent asthma. *Br J Clin Pharmacol*. 2004;58(1):26-33.	-CIC 400 mcg QD_{AM} (ex-valve, 320 mcg ex-actuator) -FP 250 mcg BID (ex-valve, 220 mcg ex-actuator)	4 weeks	N=28 Adults
Lee DKC, Fardon TC, Bates CE, Haggart K, McFarlane LC, Lipworth, BJ. Airway and systemic effects of hydrofluoroalkane formulations of high-dose ciclesonide and fluticasone in moderate persistent asthma. *CHEST*. 2005;127:851-860.	-CIC 160 mcg BID -FP 220 mcg BID	4 weeks	N=20 Adults (mean age: 47 years)
Lipworth BJ, Kaliner MA, LaForce CF, et al. Effect of ciclesonide and fluticasone on hypothalamic-pituitary-adrenal axis function in adults with mild-to-moderate persistent asthma. *Ann Allergy Asthma Immunol*. 2005;94:465-472.	-CIC 320 mcg QD_{PM} -CIC 320 mcg BID -FP 440 mcg BID -PLB	12 weeks	N=164 18 years of age and older
Magnussen H, Hofman J, Staneta P, Lawo J-P, Hellwig M, Engelstatter R. Similar efficacy of ciclesonide once daily versus fluticasone propionate twice daily in patients with persistent asthma. *J Asthma*. 2007;44:555-563.	-CIC 80 mcg QD_{PM} -CIC 160 mcg QD_{PM} -FP 88 mcg BID	12 weeks	N=808 12-75 years of age

Appendix 2: Studies Included in the Cochrane Review of CIC vs. Competitor ICS (continued)

Reference	Treatment Arms	Duration	Population
Niphadkar P, Jagannath J, Joshi JM, et al. Comparison of the efficacy of ciclesonide 160 µg QD and budesonide 200 µg BID in adults with persistent asthma: A phase III, randomized, double-dummy, open-label study. *Clin Ther*. 2005;27:1752-1763.	-CIC 160 mcg QD_{AM} -CIC 160 mcg QD_{PM} -BUD 200 mcg BID (ex-valve)	12 weeks	N=405 18-69 years of age
Pedersen S, Garcia ML, Manjra A, Theron I, Engelstatter R. A comparative study of inhaled ciclesonide 160 µg/day with fluticasone propionate 176 µg/day in children with asthma. *Pediatr Pulmonol*. 2006. 41:954-961.	-CIC 80 mcg BID -FP 88 mcg BID	12 weeks	N=556 6-15 years of age
Ukena D, Biberger C, Steinijans V, et al. Ciclesonide is more effective than budesonide in the treatment of persistent asthma. *Pulm Pharmacol Ther*. 2007;20:562-570.	-CIC 320 mcg QD_{PM} -BUD 400 mcg QD_{PM}	12 weeks	N=399 12-75 years of age
Vermeulen JH, Gyurkovits K, Rauer H, Engelstätter R. Randomized comparison of the efficacy and safety of ciclesonide and budesonide in adolescents with severe asthma. *Respir Med*. 2007;101:2182-2191.	-CIC 320 mcg QD_{PM} -BUD 800 mcg QD_{PM} DPI	12 weeks	N=403 12-17 years of age
von Berg A, Engelstätter R, Minic P, et al. Comparison of the efficacy and safety of ciclesonide 160 µg once daily vs. budesonide 400 µg once daily in children with asthma. *Pediatr Allergy Immunol*. 2007:18:391–400.	-CIC 160 mcg QD_{PM} -BUD 400 mcg QD_{PM} (ex-valve)	12 weeks	N=621 6-11 years of age
Zietkowski Z, Bodzenta-Lukaszyk A, Tomasiak MM, Szymanski W, Skiepko R. Effect of ciclesonide and fluticasone on exhaled nitric oxide in patients with mild allergic asthma. *Respir Med*. 2006;100:1651-1656.	-CIC 80 mcg QD_{PM} -CIC 160 mcg QD_{PM} -FP 100 mcg BID (ex-valve)	12 weeks	N=35 Adults

DB denotes double-blind, PG- parallel-group, OL- open label, CIC- ciclesonide, BDP- beclomethasone dipropionate, PLB- placebo, BUD- budesonide, FP- fluticasone propionate

3. Modeling Report

At the time that this dossier went to press, modeling reports for ALVESCO Inhalation Aerosol have not been developed.

4. ALVESCO Value and Overall Cost

Asthma is a significant health burden in the United States. In 2003, asthma resulted in 12.8 million missed days of school and 10.1 million days of work annually. In 2005, 22.2 million people were diagnosed with asthma and over 12 million people with asthma had experienced an exacerbation during the previous year. For almost 500,000 of those people, their exacerbation was severe enough that it could not be controlled at home or in a doctor's office and required hospitalization.[CDC website]

According to the National Institute of Health (NIH) guidelines, treatment of asthma with an inhaled corticosteroid (ICS) is the preferred therapy for long-term control of asthma inflammation and symptoms. NIH guidelines recommend that a goal of asthma therapy is to maintain control of asthma with the least amount of medication possible. Once asthma is diagnosed, the appropriate pharmacotherapy is determined by assessing disease severity, based on the domains of impairment and risk. For all steps other than mild intermittent asthma, treatment with inhaled corticosteroids is recommended as first-line therapy either as monotherapy or in combination with other agents such as long-acting beta-agonists. For all steps, a short-acting beta-agonist should be used as needed.[NHLBI EPR-3]

Despite the availability and benefits of ICS therapy, many patients are not achieving the goals of therapy (improvements in the domains of impairment and risk). The Asthma in America survey performed in 1998 included 1,788 adults (subjects over 16 years of age) and 721 children with asthma, who were surveyed by telephone about their experience with asthma.[1] The survey found that 30% of subjects had sleep disruption due to asthma at least once a week, 32% had missed work or school in the past year due to asthma, 48% limited participation in sports or other activities due to asthma, and 23% had had an unscheduled emergency department visit in the past year due to asthma.[Chipps]

One of the main reasons for failure to achieve the goals of asthma is the underuse of ICS therapy due to underprescribing and poor patient adherence. In one survey of 509 adult asthmatics, only 67% of patients were prescribed ICS therapy for their moderate to severe asthma.[Ulrik] Even when ICS are prescribed, patients do not comply with long-term therapy for a variety of reasons. Patients often have poor perception of control, and may underestimate the degree of airway obstruction they are experiencing.[NHLBI EPR-3] In a study done in predominantly low income, non-white patients, some patients believe that when symptoms are not present, they do not have asthma and therefore do not need to stay on therapy.[Halm] Patients may have safety concerns about taking corticosteroids, even via the inhaled route.[Ulrik] Patients may often overuse rescue therapy due to the severity of their symptoms while underusing controller therapy when symptoms abate.[Diette] This type of behavior suggests that patients are often taking the medications that immediately relieve their symptoms rather than the maintenance medications that provide long-term control.

The important economical impact of the use of inhaled corticosteroids as maintenance therapy in patients with asthma has been evaluated. A retrospective review of the direct costs associated with patients with mild persistent asthma in relation to the pattern of inhaled corticosteroid use during the period of January 1999 to December 2003 was performed using the administrative claims submitted for the employees, spouses, and dependents of 17 large self-insured U.S. companies. This cost evaluation included inhaled corticosteroids other than ciclesonide due to the fact that it was not available in the U.S. at that time. Inhaled corticosteroid (ICS) use was determined using claims history (no/low usage- 0 to 2 claims per evaluation time period, consistent usage- 3 or more claims per evaluation time period). Direct healthcare costs were higher for patients with no/low ICS usage ($4,952) compared to consistent ICS usage ($3,747, $p<0.05$). The excess medical cost was due mostly to increased hospital costs in the no/low ICS usage group. Asthma-specific healthcare cost was higher in patients with no/low ICS use ($1,332) compared to consistent ICS use ($789, $p<0.01$). Asthma-specific drug cost for both groups was similar (no/low ICS- $552 vs. consistent ICS- $591, $p>0.05$).[Colice]

As discussed in more detail in the Clinical Trial overview section, results from clinical trials with ALVESCO Inhalation Aerosol taken twice-daily demonstrated that ALVESCO Inhalation Aerosol:

- Improved respiratory parameters (including AM pre-dose FEV_1, AM PEF, rescue medication use, and total asthma symptom scores) with adverse events comparable to placebo in patients with mild to moderate persistent asthma that were previously treated with bronchodilators only[DOF 3031]
- Maintained improvements in respiratory parameters (including AM pre-dose FEV_1, AM PEF, rescue medication use, and total asthma symptom scores) with adverse events comparable to placebo in patients with mild to moderate persistent asthma that were switched from a maintenance ICS to ALVESCO[DOF 3030]
- Maintained improvements in respiratory parameters (including AM pre-dose FEV_1, AM PEF, rescue medication use, and total asthma symptom scores) with adverse events comparable to placebo in patients with moderate to severe persistent asthma that were switched from a maintenance ICS to ALVESCO[DOF 323/324]
- Maintained improvements in respiratory parameters (including AM pre-dose FEV_1, AM PEF, rescue medication use, and total asthma symptom scores) with adverse events comparable to placebo in patients with severe persistent asthma that were switched to ALVESCO and resulted in a significant percentage of patients reporting a decrease and/or elimination of maintenance oral corticosteroids[DOF 325]
- A significant improvement in overall quality of life compared to placebo[DOF321,322,323/324]

As a safe and effective treatment in the maintenance of persistent asthma, ALVESCO represents an important addition to the class of inhaled corticosteroids. The wholesale acquisition cost for ALVESCO is shown in **Table 4.1.1**:

Table 4.1.1: ALVESCO Availability and Prices

Micrograms per Inhalation	Number of Inhalations per Canister	Canister Weight	NDC Number	WAC*
ALVESCO 80 mcg	60	6.1g	63402-711-01	$130.00
ALVESCO 160 mcg	60	6.1g	63402-712-01	$130.00

*Wholesaler acquisition cost.

5. Supporting Information

References

Bolded references are included as enclosures. To request references not enclosed, please contact Sepracor Medical Information (1-800-739-0565).

Adachi M, Ishihara K, Inoue H, et al. Efficacy and safety of inhaled ciclesonide compared with chlorofluorocarbon beclomethasone dipropionate in adults with moderate to severe persistent asthma. *Respirology.* 2007;12:573-580.

Advair® (fluticasone propionate and salmeterol inhalation powder) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; April 2008.

Aerobid® (flunisolide) Inhaler System [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc; Mar 2002.

ALVESCO® (ciclesonide) Inhalation Aerosol [package insert]. Marlborough, Mass: Sepracor Inc; July 2008.

American Lung Association. Trends in asthma morbidity and mortality. New York, NY: November 2007.

Asmanex® Twisthaler (mometasone furoate inhalation powder) [package insert]. Kenilworth, NJ: Schering Corporation; Feb 2008.

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